

Cancer-Enabling Inflammation

How inflammatory and stromal cells support malignant progression

Tumor microenvironment • mechanisms • clinical interpretation

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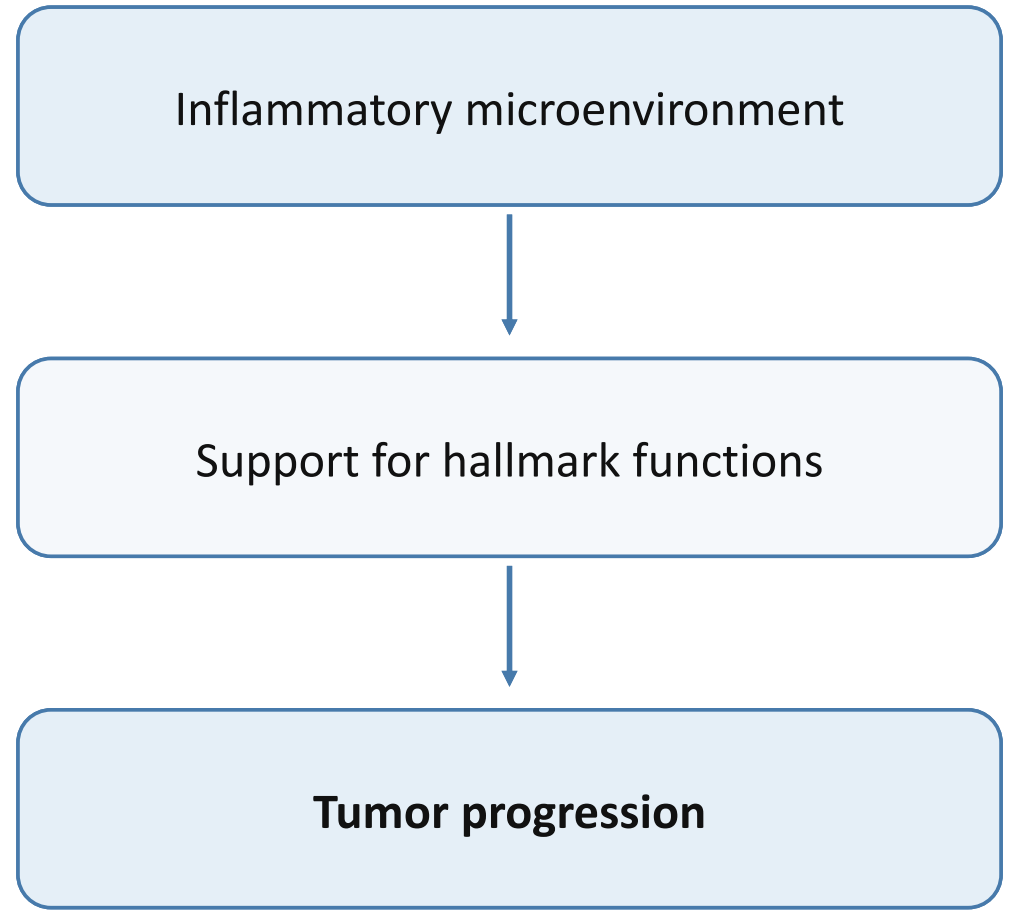
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Learning objectives

- Identify the cellular participants in tumor-associated inflammation.
- Explain six proposed mechanisms that enable cancer hallmarks.
- Differentiate protumor inflammation from effective antitumor immunity.
- Interpret macrophage polarization and therapeutic implications critically.

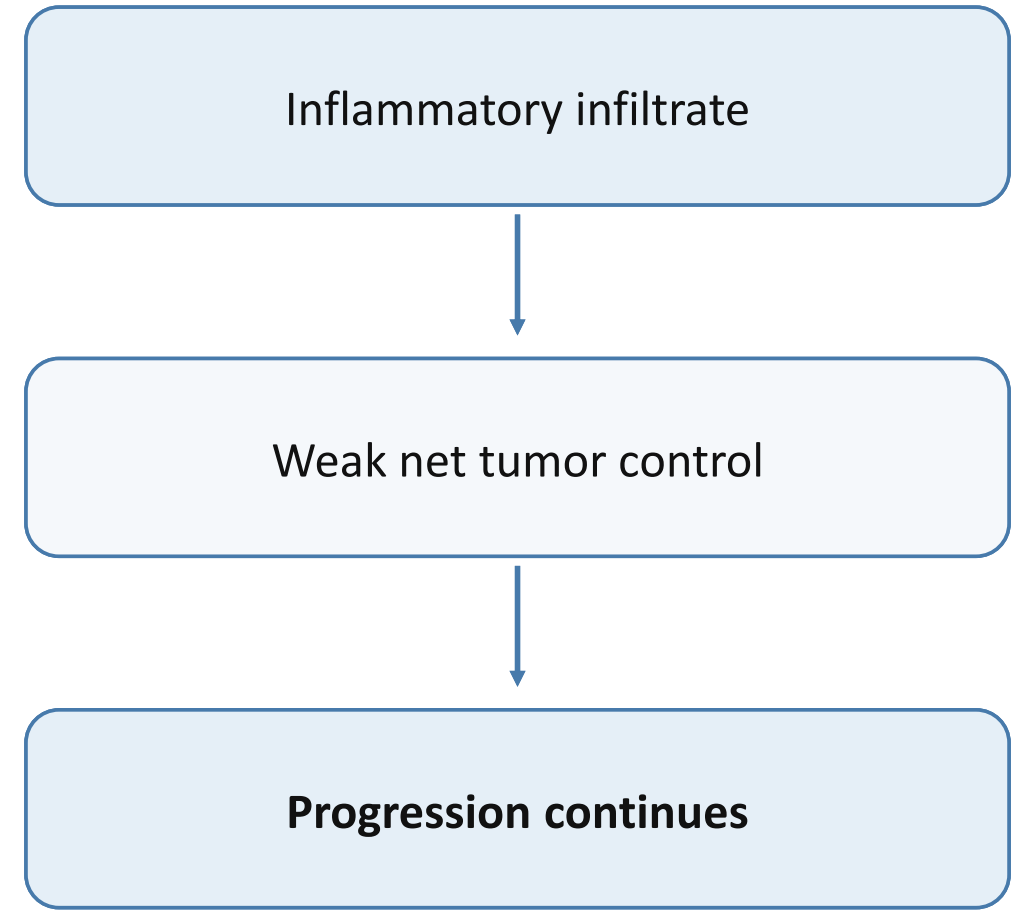
Inflammation is an enabling characteristic

- Cancer-promoting inflammation facilitates acquisition or expression of other hallmarks.
- It is an enabling condition, not a synonymous label for malignancy.
- Its effects arise through tumor–host interactions.



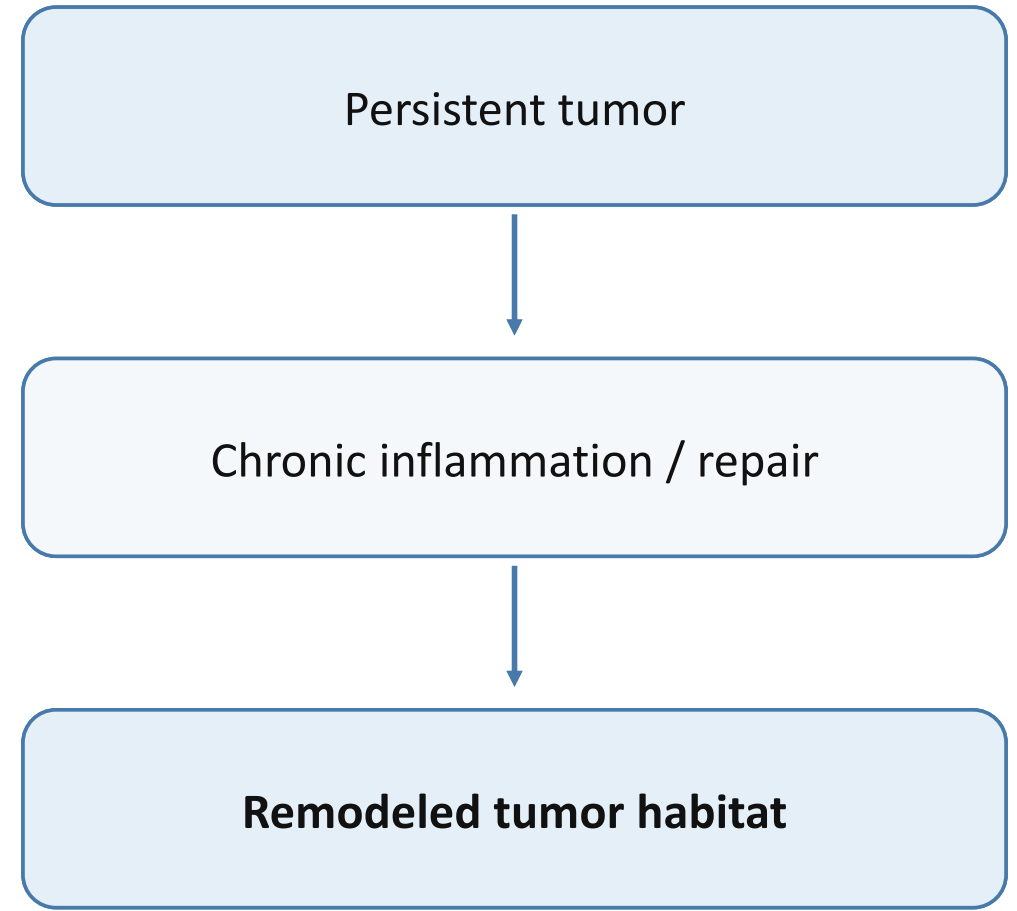
A paradox: Abundant inflammation, ineffective restraint

- Infiltrating cancers frequently provoke chronic inflammatory reactions.
- The reaction can coexist with continued malignant expansion.
- Cellular presence does not establish successful tumor-cell killing.



“Wounds that do not heal”

- The textbook uses a persistent-wound analogy for infiltrating cancers.
- Inflammatory and repair programs may remain active around the tumor.
- Unlike successful repair, the malignant stimulus persists.



Causal interpretation requires restraint

Experimental support

Tumor–stroma cross-talk

Causal pathways in models

Clinical interpretation

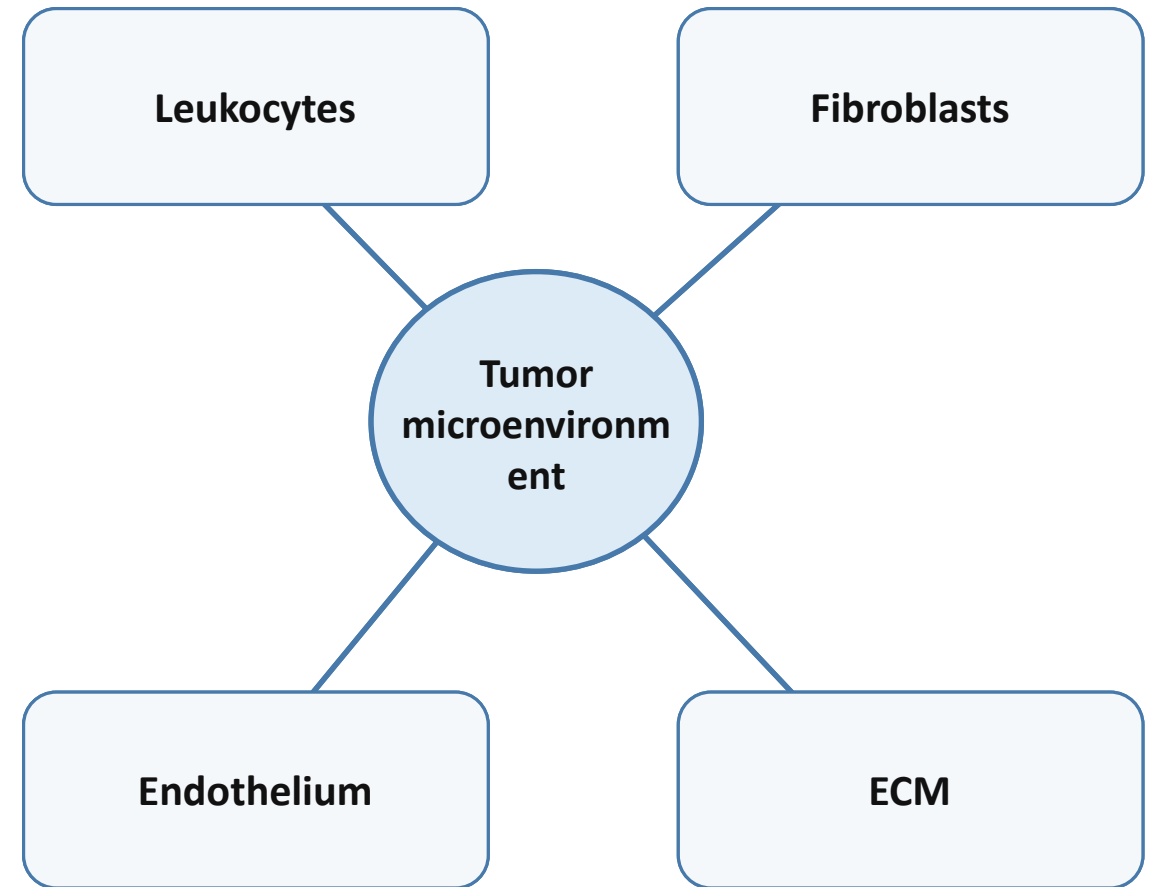
Human tumor heterogeneity

Do not infer individual prognosis

- Multiple cancer-enabling effects as proposed mechanisms.
- Much supporting mechanistic evidence comes from animal models.
- The contribution of each pathway varies with cellular context.

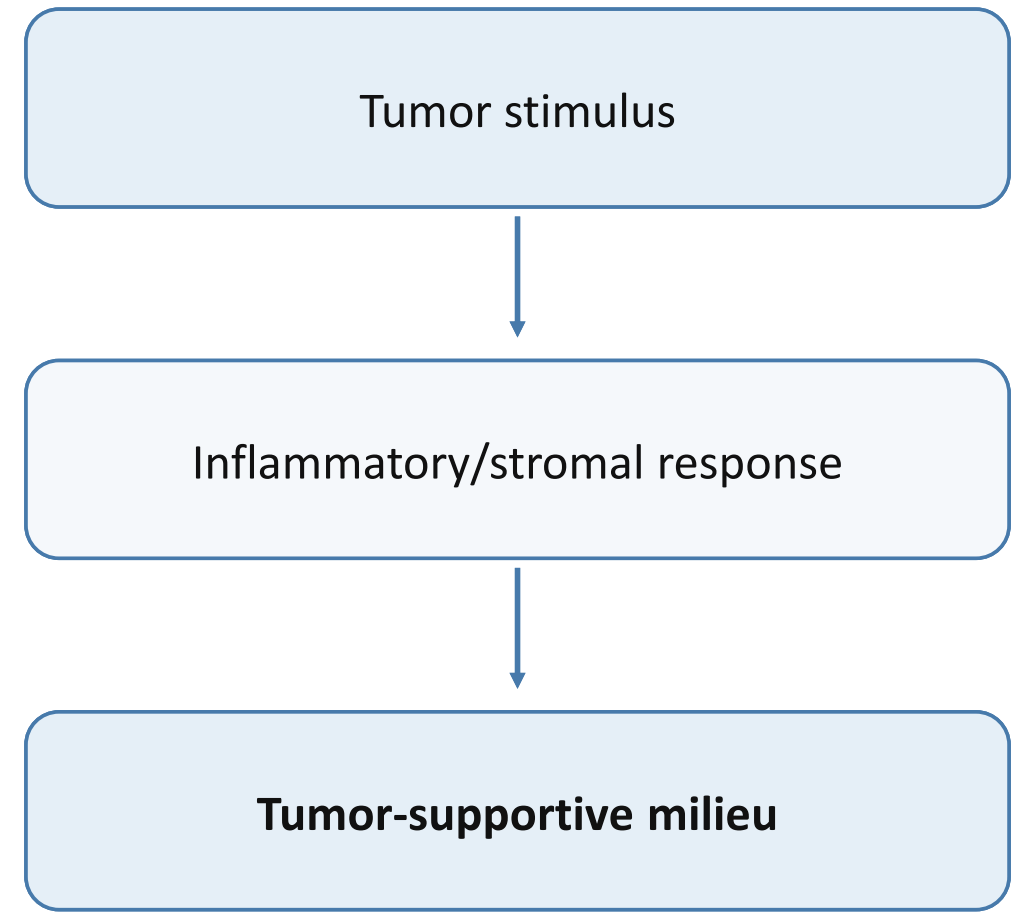
The tumor microenvironment is multicellular

- Tumor cells coexist with infiltrating leukocytes and resident stromal cells.
- Fibroblasts and endothelial cells are active signaling partners.
- Extracellular matrix (ECM) is both scaffold and source of signals.



Bidirectional tumor–stroma communication

- Cancer cells provoke a chronic local inflammatory reaction.
- Inflammatory/stromal cells release mediators and remodel the ECM.
- The resulting tissue environment feeds back on tumor behavior.



Local versus systemic effects

Local tissue

Proliferation and invasion

Angiogenesis and immune escape

Systemic illness

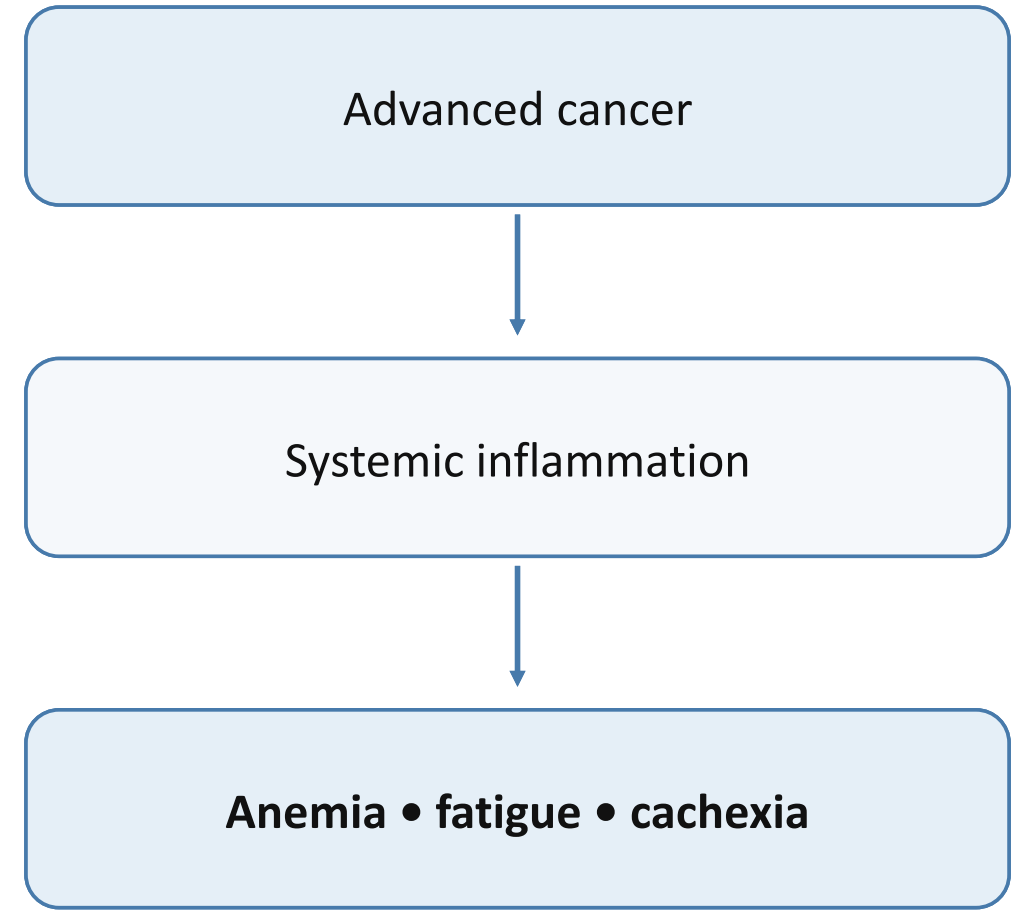
Anemia

Fatigue and cachexia

- Locally, growth, invasion, blood vessels, and immune function can change.
- In advanced cancer, inflammation may produce systemic manifestations.
- These are distinct outcomes of a related inflammatory process.

Systemic manifestations of advanced cancer

- Inflammation in advanced disease may contribute to anemia.
- Fatigue and cachexia may accompany the systemic reaction.
- These symptoms do not measure the success of antitumor immunity.

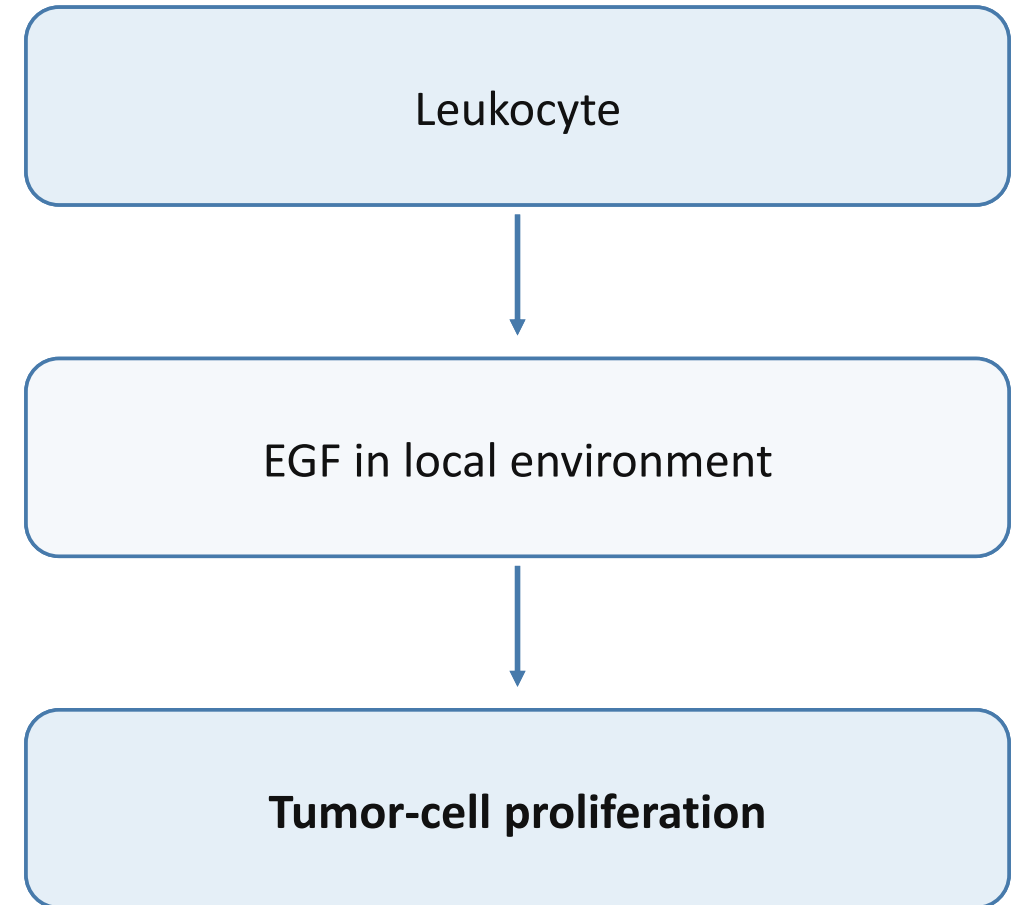


Six tumor-enabling outputs

Cancer-enabling output	Principal source-described mechanism
More proliferation	EGF; ECM-liberated growth factors
Fewer growth restraints	Proteolysis of adhesion interfaces
Improved survival	Macrophage contact; stromal survival signals
More blood vessels	Inflammatory VEGF
Invasion / migration	ECM remodeling; TNF/EGF; TGF- β
Immune escape	Tregs, CD8 suppression, macrophage PD-L1

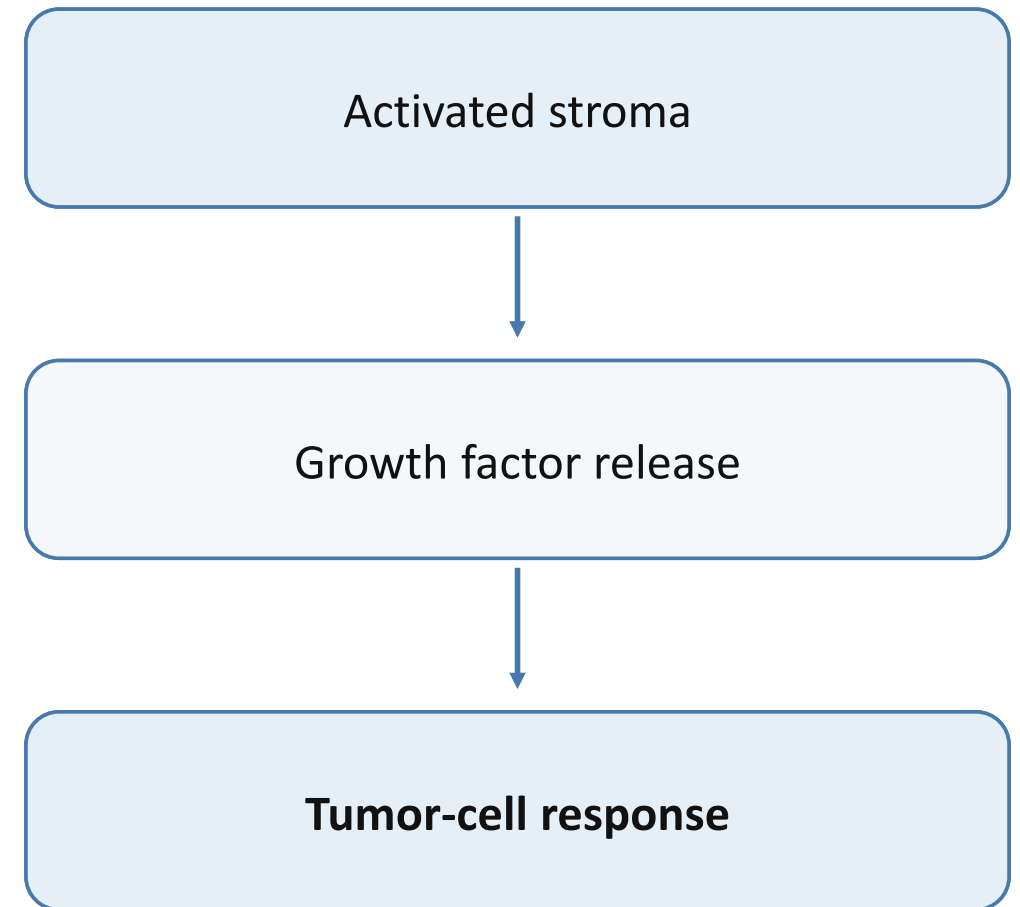
Inflammatory cells supply growth factors

- Infiltrating leukocytes can secrete growth-promoting mediators.
- EGF is the named example in the cancer-inflammation section.
- This is a paracrine route to growth support.



Activated stromal cells contribute to proliferation

- Activated stromal cells are additional producers of growth factors.
- The malignant clone is therefore not the only source of proliferative signals.
- The influence depends on proximity and responsiveness.



Paracrine support does not require a new driver mutation

Tumor-intrinsic

Altered signaling inside cancer cell

Oncogene-related growth

Microenvironmental

Signal supplied by host cells

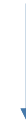
EGF and related factors

- A growth-promoting signal may originate outside the malignant cell.
- This differs conceptually from oncogene-driven constitutive growth.
- Environmental inputs can cooperate with tumor-intrinsic alterations.

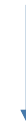
The extracellular matrix stores biologic signals

- The ECM provides structural support and binds molecules in tissue.
- Proteolysis can liberate growth factors from the matrix.
- Matrix remodeling may therefore change both architecture and signaling.

Growth factors associated with ECM



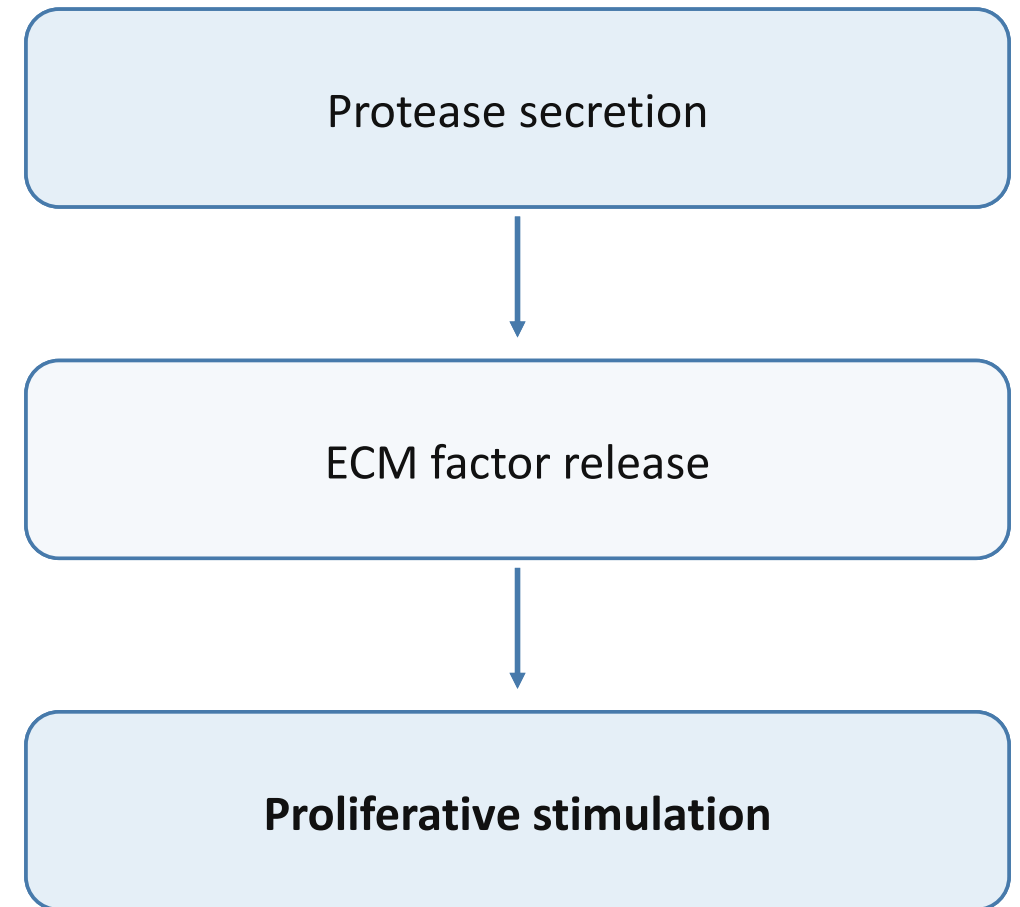
Inflammatory proteases



Released growth signal

Proteases amplify growth indirectly

- Inflammatory-cell proteases act on the extracellular environment.
- Liberated ECM-associated factors can augment proliferation.
- The enzyme need not be a direct mitogen to support growth.



Two routes converge on proliferation

Direct

Leukocyte / stromal factor

EGF → tumor cell

Indirect

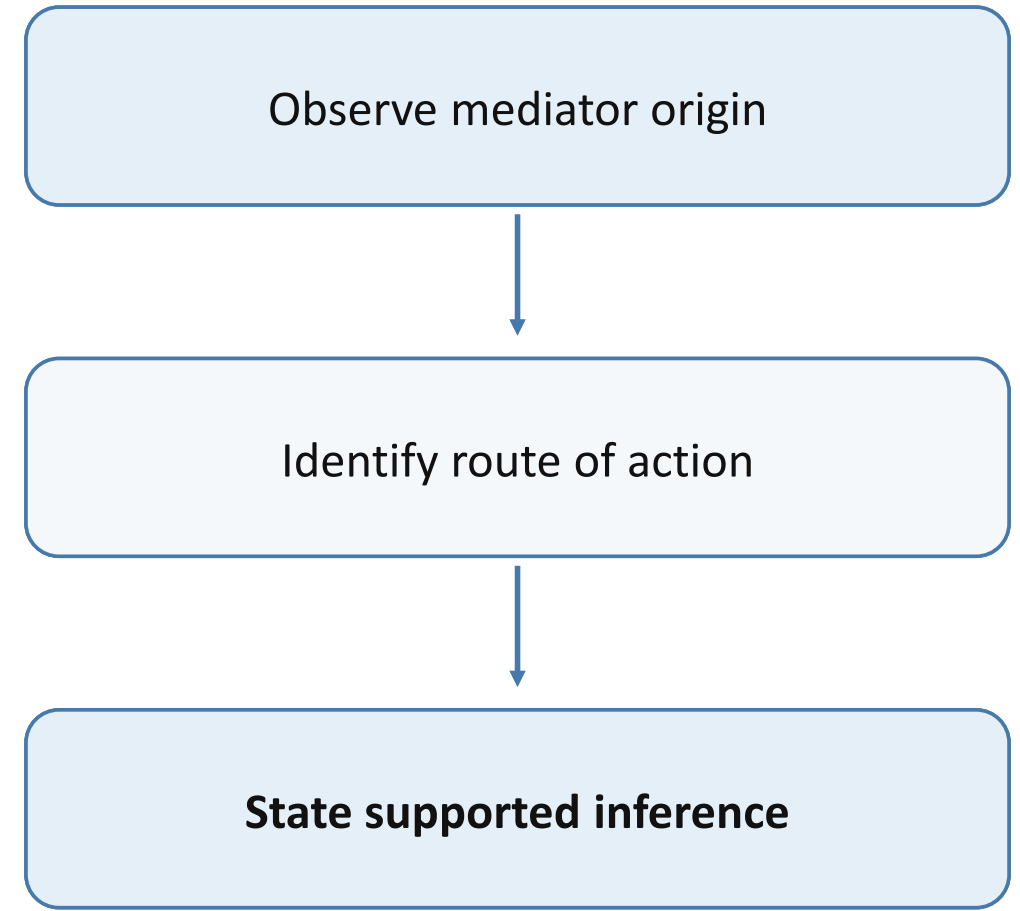
Protease acts on ECM

Factor release → tumor cell

- Direct route: Cells secrete growth factors such as EGF.
- Indirect route: Proteases release matrix-associated growth factors.
- Both modify external signals available to cancer cells.

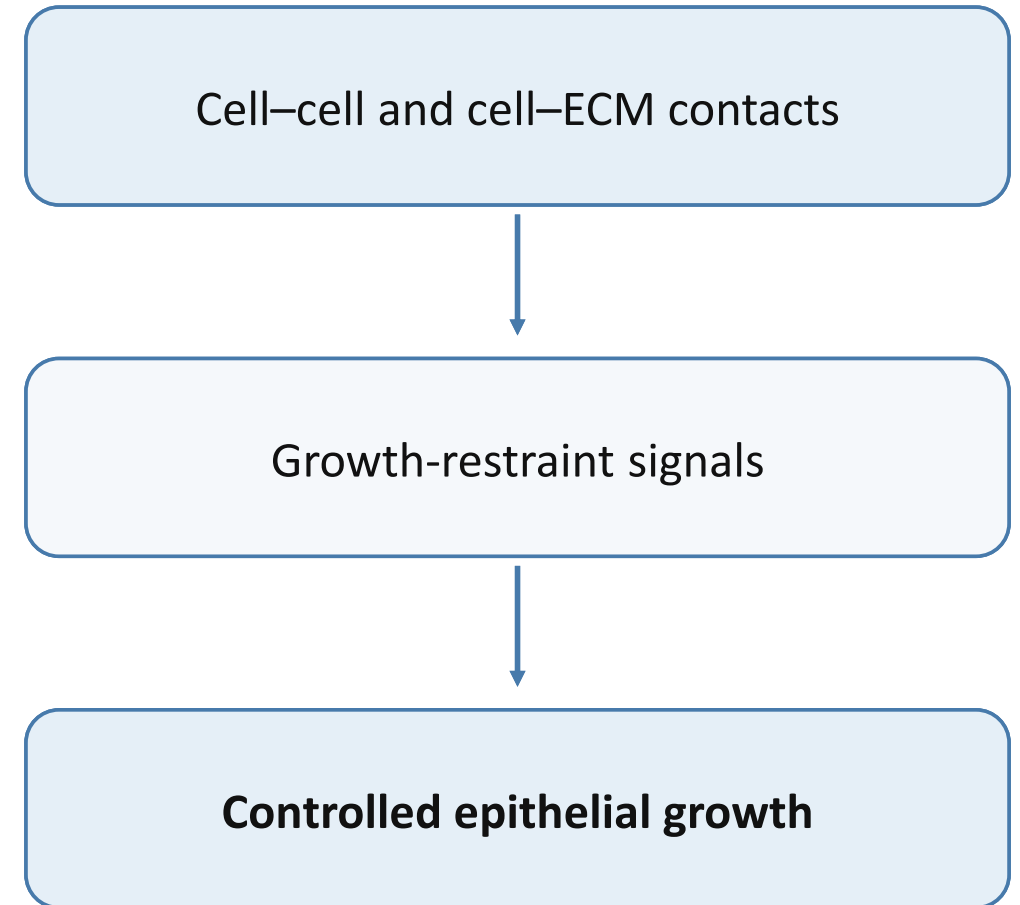
Growth-support mechanism: Apply the distinction

- An inflammatory infiltrate expresses a growth factor: Direct paracrine support.
- Protease-rich stroma releases matrix-bound factors: Indirect support.
- Neither observation alone proves that inflammation initiated the cancer.



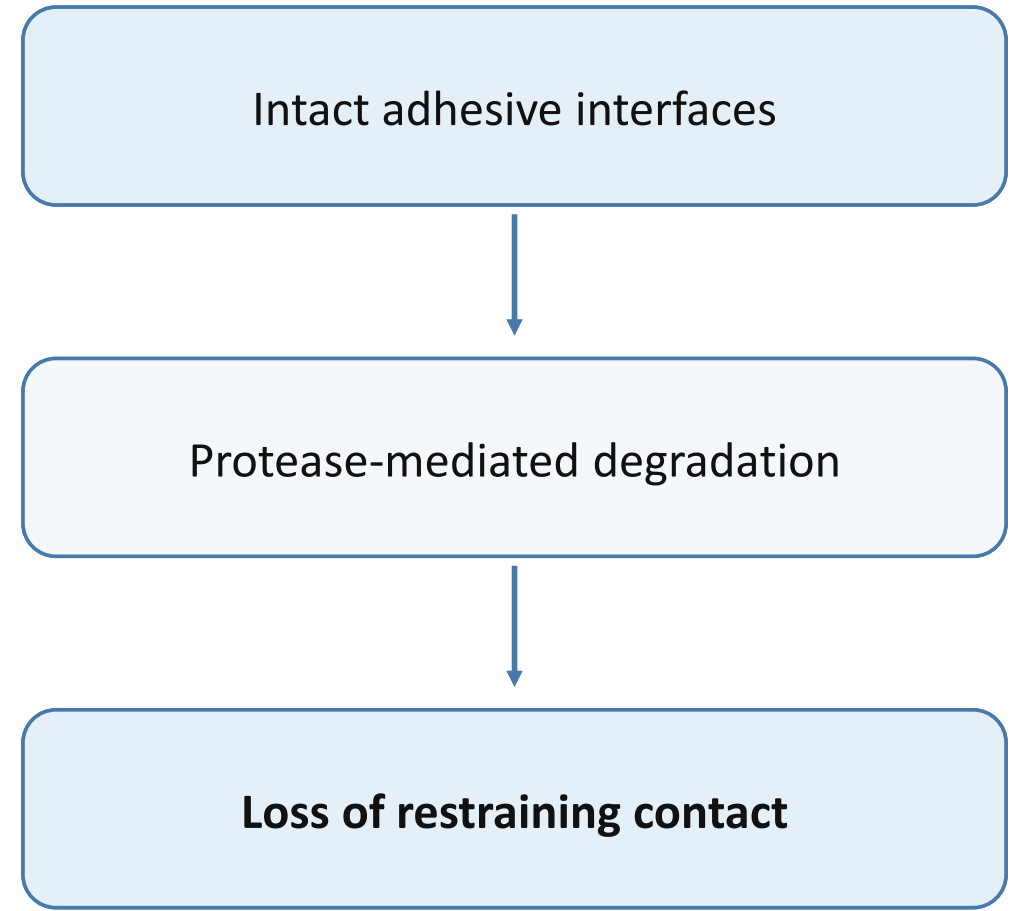
Normal epithelia receive growth-inhibitory cues

- Interactions between adjacent epithelial cells help restrain expansion.
- Epithelial attachment to the ECM also helps regulate growth.
- These structural interactions participate in tissue homeostasis.



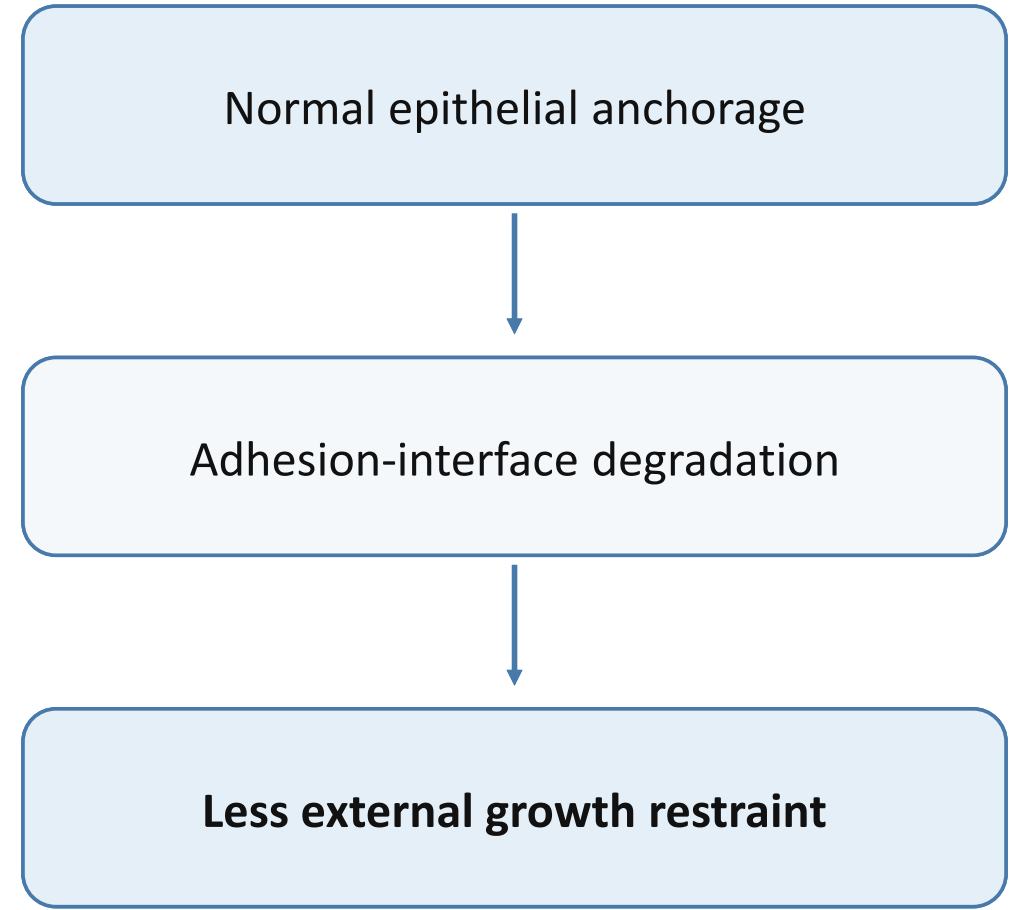
Cell–cell adhesion is a regulatory interface

- Adhesion molecules connect neighboring epithelial cells.
- Their function extends beyond simply holding tissue together.
- Proteolytic disruption can remove a normal growth barrier.



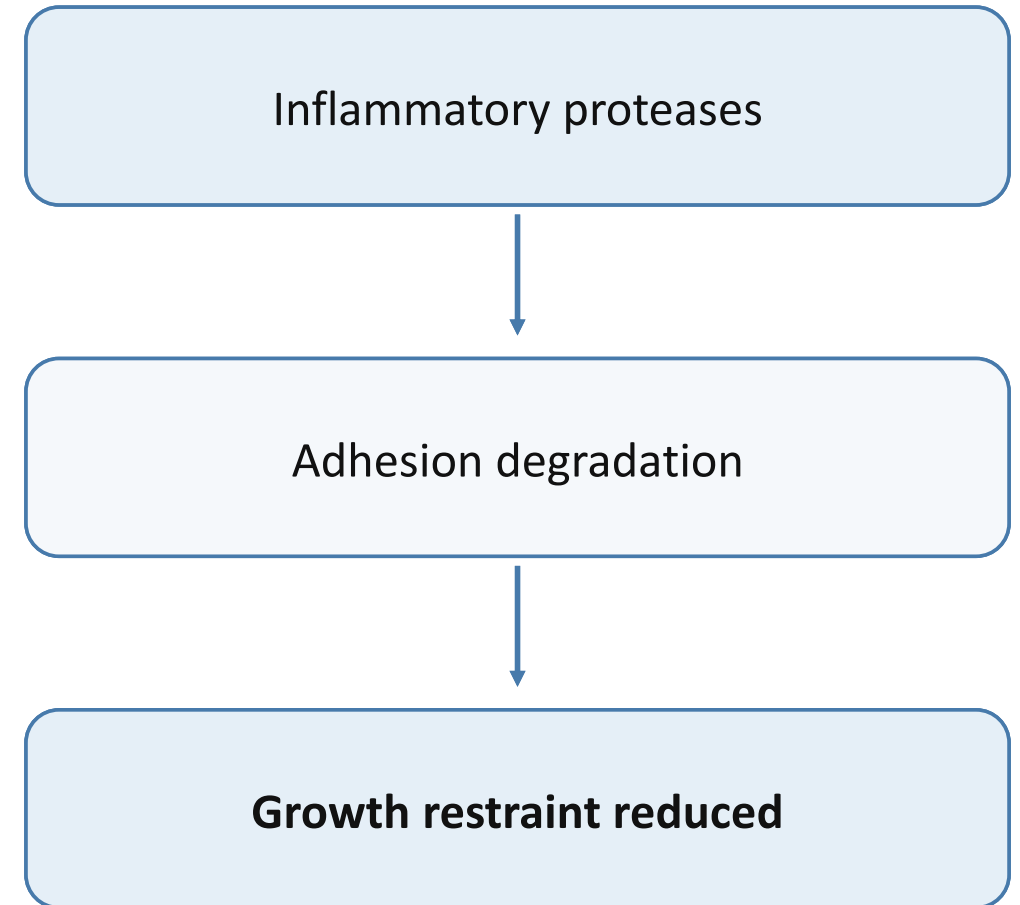
Cell–ECM adhesion also restrains proliferation

- Attachment to ECM contributes to epithelial organization.
- Inflammatory proteases can disrupt molecules mediating this attachment.
- Disruption may favor abnormal expansion.



Proteolysis can remove growth suppressors

- Leukocyte-derived proteases degrade adhesion molecules.
- The consequence is loss of suppressive cell–cell and cell–ECM cues.
- This is environmental disinhibition rather than gene deletion.



Growth suppression: Gene versus tissue context

Intrinsic control

Genetic alteration in cell

Defective checkpoint/signaling

Extrinsic control

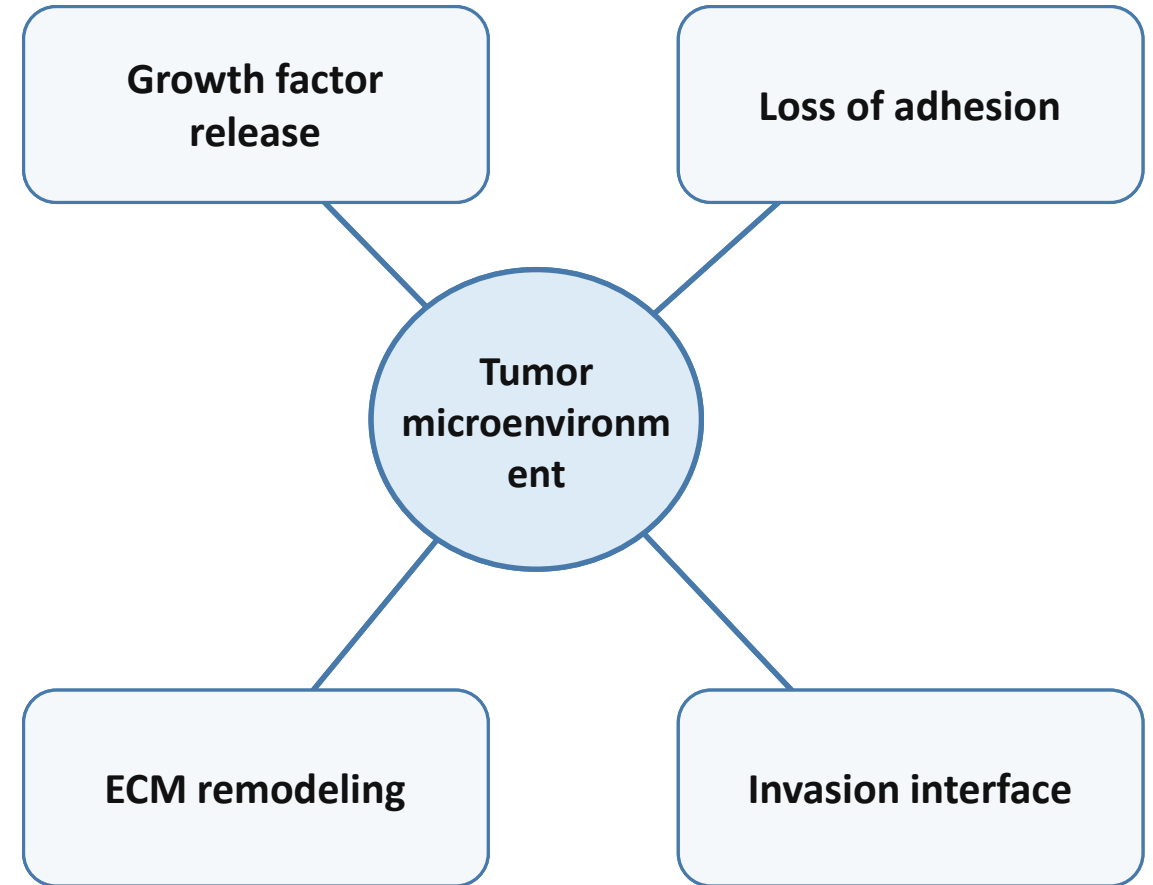
Proteases in adjacent stroma

Disrupted adhesive restraint

- Tumor-suppressor gene defects alter intrinsic regulatory programs.
- Microenvironmental proteolysis changes external growth restraints.
- Both may support growth, but they are not identical mechanisms.

The same protease can affect several hallmarks

- Adhesion degradation weakens normal growth restraint.
- ECM cleavage releases stored growth factors.
- Matrix remodeling may also facilitate tumor invasion.



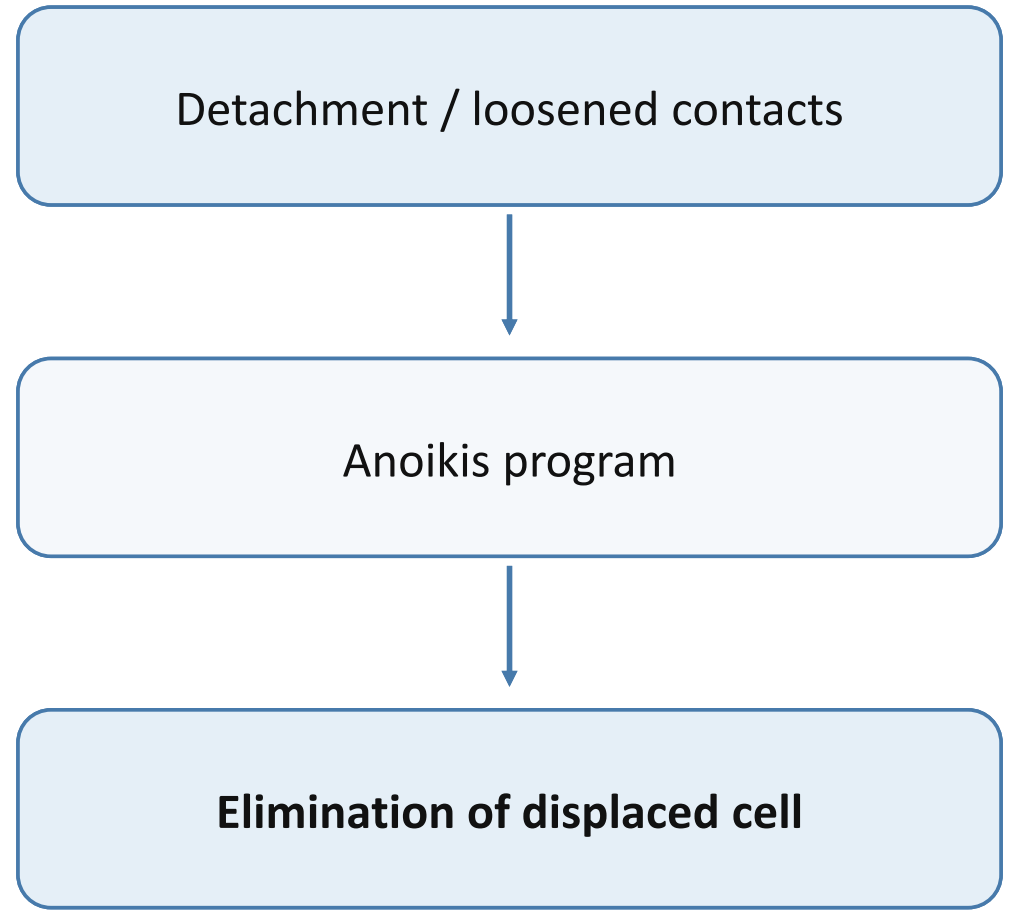
Structural integrity versus invasive remodeling

Organized tissue	Remodeled tissue
Basement membrane intact	Proteolytic activity
Adhesion constraints maintained	Altered signaling and barrier function

- Organized epithelia preserve boundaries and cell contacts.
- Protease-active stroma disrupts parts of the matrix environment.
- The functional consequence depends on what is degraded and where.

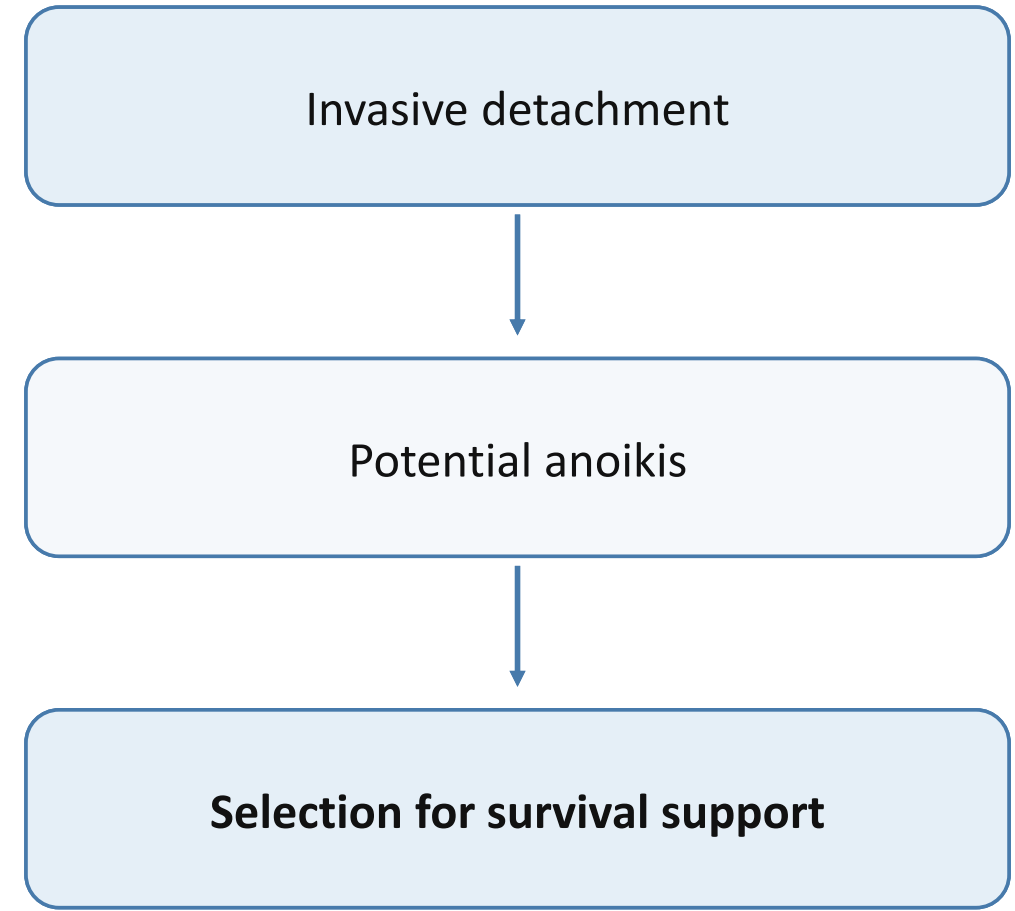
Anoikis couples survival to attachment

- Anoikis is cell death associated with detachment from basement membrane.
- Loss of cell–cell interactions can also favor anoikis.
- This protects against inappropriate survival of displaced epithelial cells.



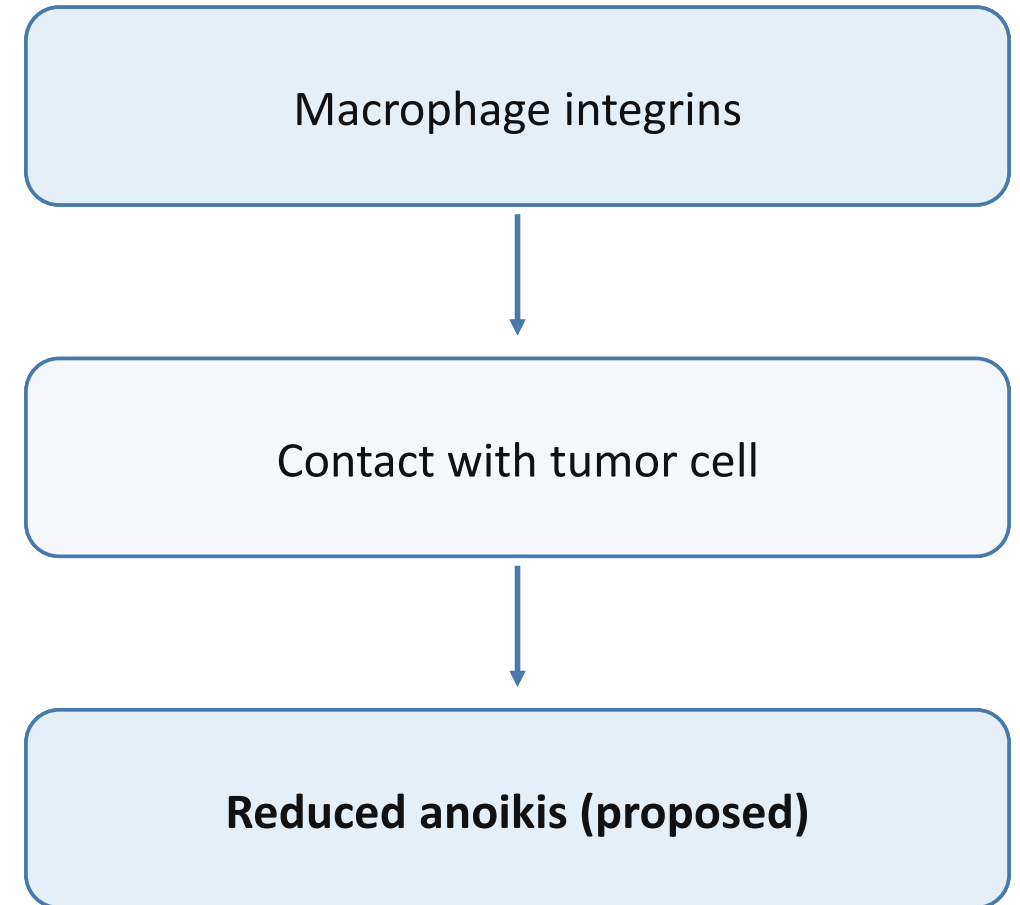
Why detachment is a problem for a cancer cell

- Invasion requires cells to loosen attachment to neighbors or ECM.
- Such detachment would ordinarily expose cells to anoikis.
- Survival during this transition requires additional support.



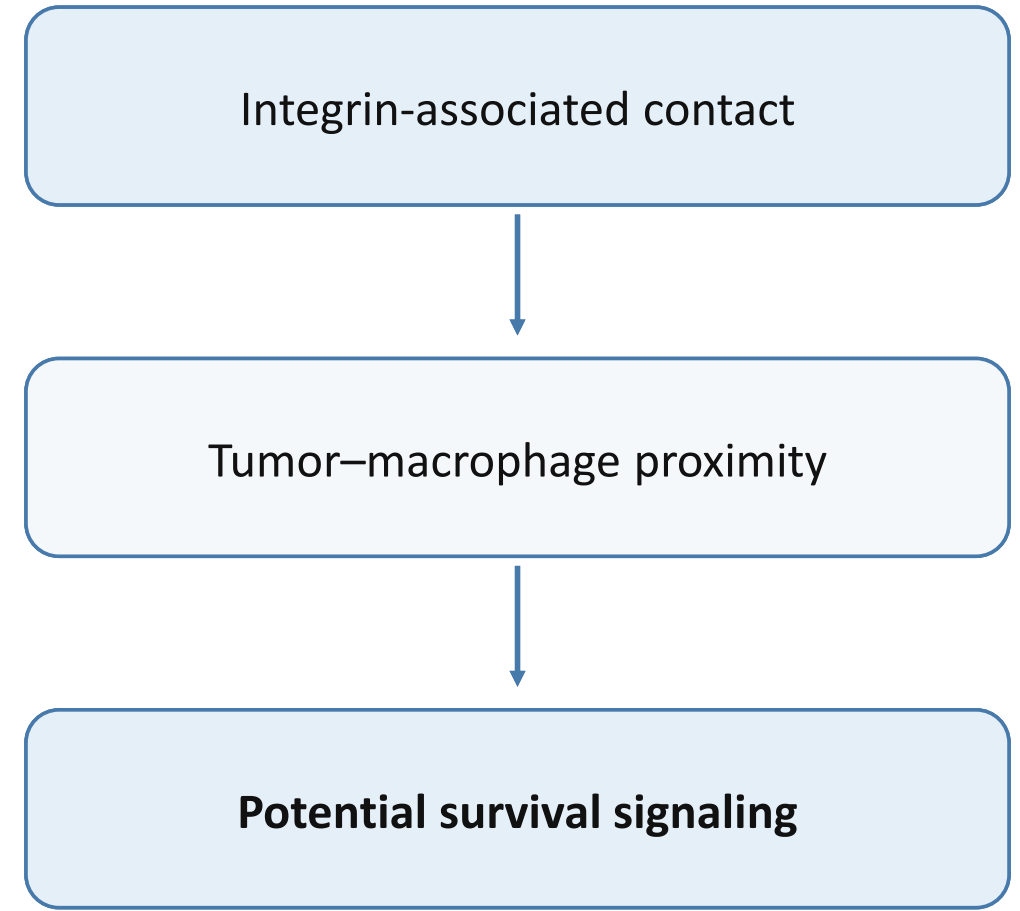
Tumor-associated macrophages may blunt anoikis

- A protective role for tumor-associated macrophages.
- Macrophage integrins may mediate physical contact with cancer cells.
- The suggested result is improved survival despite disrupted anchorage.



Macrophage contact is a physical signal

- The proposed mechanism involves adhesion, not only soluble factors.
- Direct tumor–macrophage interaction may substitute for some survival cues.
- The source does not define a universal receptor pair on every cancer.



Anoikis protection: Level of confidence

Established

Detachment can induce anoikis

Epithelial cell response

Proposed

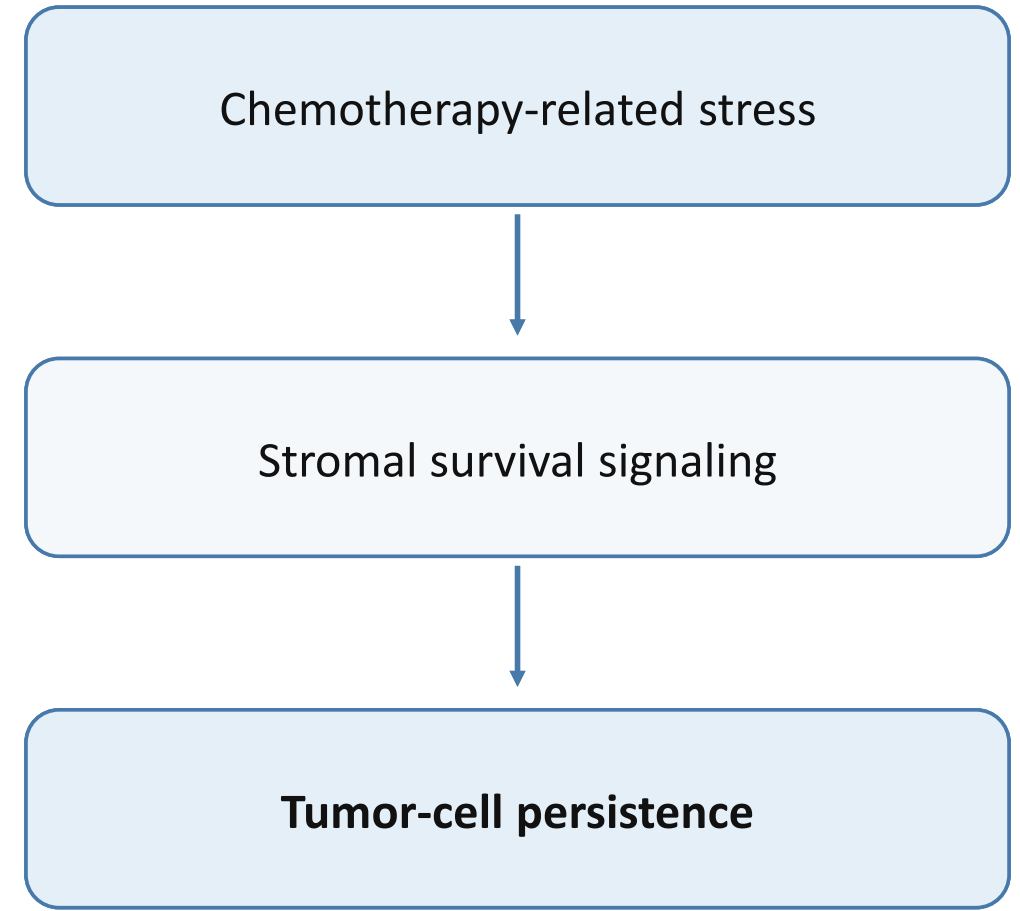
Macrophage integrin contact

Tumor-cell rescue

- Anoikis after detachment is an established epithelial response.
- Specific macrophage-mediated rescue is described as suspected.
- A mechanistic hypothesis must be distinguished from confirmed clinical benefit.

Stromal cells may protect against chemotherapy

- Tumor–stroma interactions can increase drug resistance.
- The suggested mechanism is activation of survival pathways.
- DNA-damage stress is the example emphasized.



Microenvironmental survival is not necessarily genetic resistance

Cancer cell–intrinsic	Microenvironmental
Mutation or altered cell program	Stromal survival cues
Cell autonomous	Context dependent

- Stromal protection can alter response without a new resistance mutation.
- Intrinsic tumor-genome changes are a separate source of resistance.
- A drug-response phenotype can therefore reflect both cell and context.

Two survival routes should not be conflated

Loss of anchorage

Integrin-related macrophage contact

Anoikis resistance (proposed)

DNA damage / drug stress

Stromal survival pathways

Treatment resistance

- Cell contact is proposed to protect against anoikis.
- Stromal signaling can buffer cytotoxic stress.
- Both enhance survival, but operate in different circumstances.

Survival question: Disrupted basement membrane

Detachment from ECM

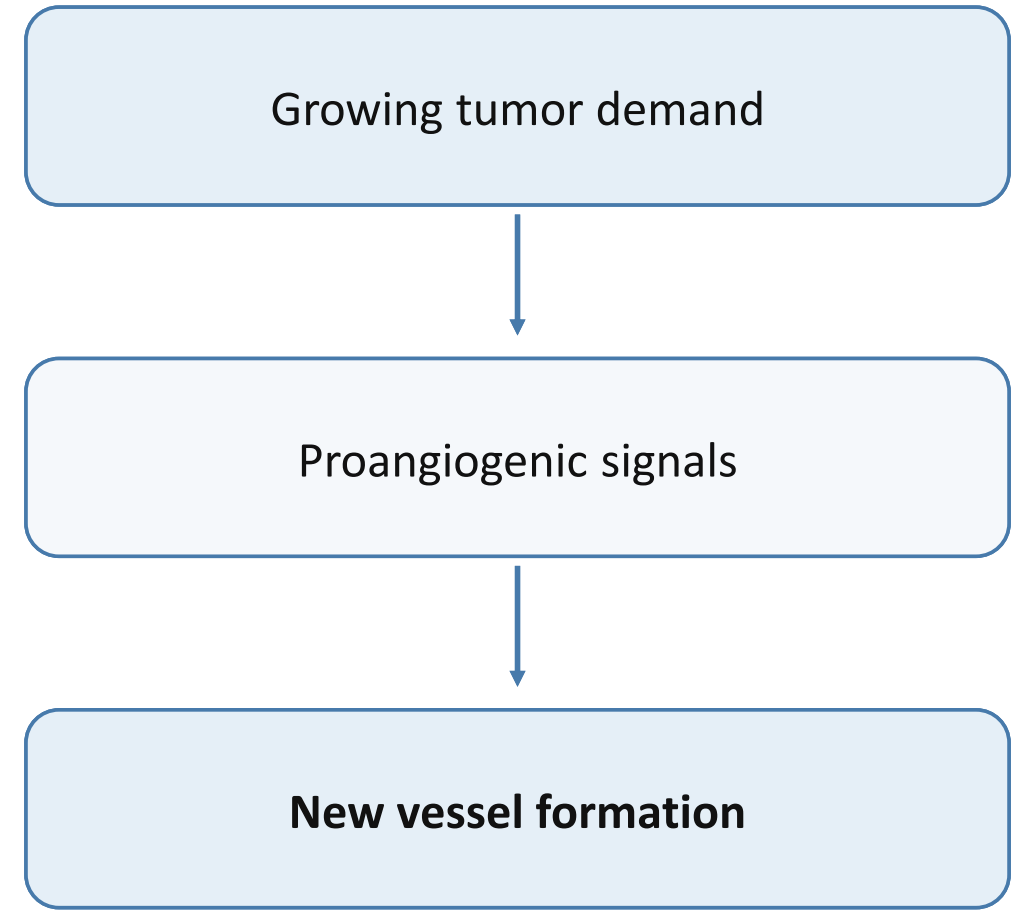
Expected: Anoikis

Proposed: Macrophage contact

Discuss the mechanistic inference and what remains unproved.

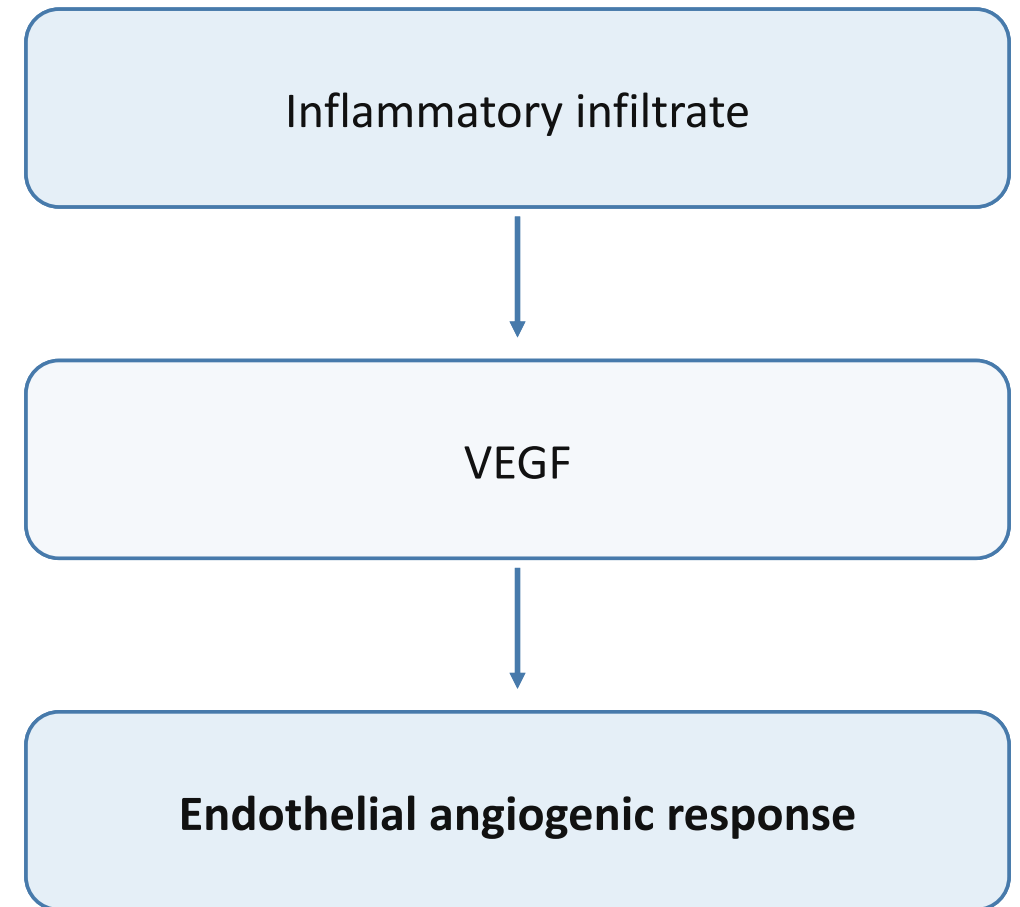
Angiogenesis supplies an expanding tumor

- Angiogenesis forms new vessels from pre-existing vasculature.
- Tumor expansion can exceed the support of the initial blood supply.
- Inflammatory cells can contribute proangiogenic signals.



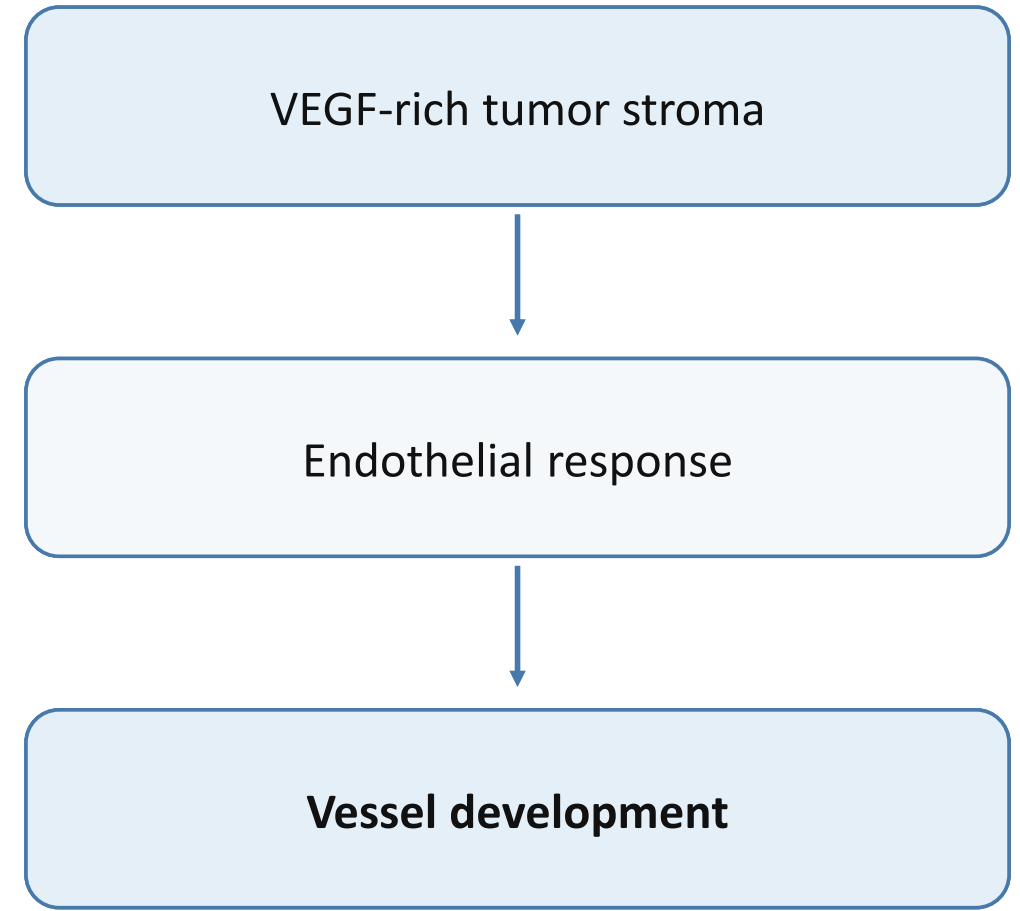
Inflammatory cells release VEGF

- VEGF is an explicit proangiogenic example in the source.
- It can act on vascular endothelial cells in the local environment.
- This links leukocyte activity to a nonimmune hallmark.



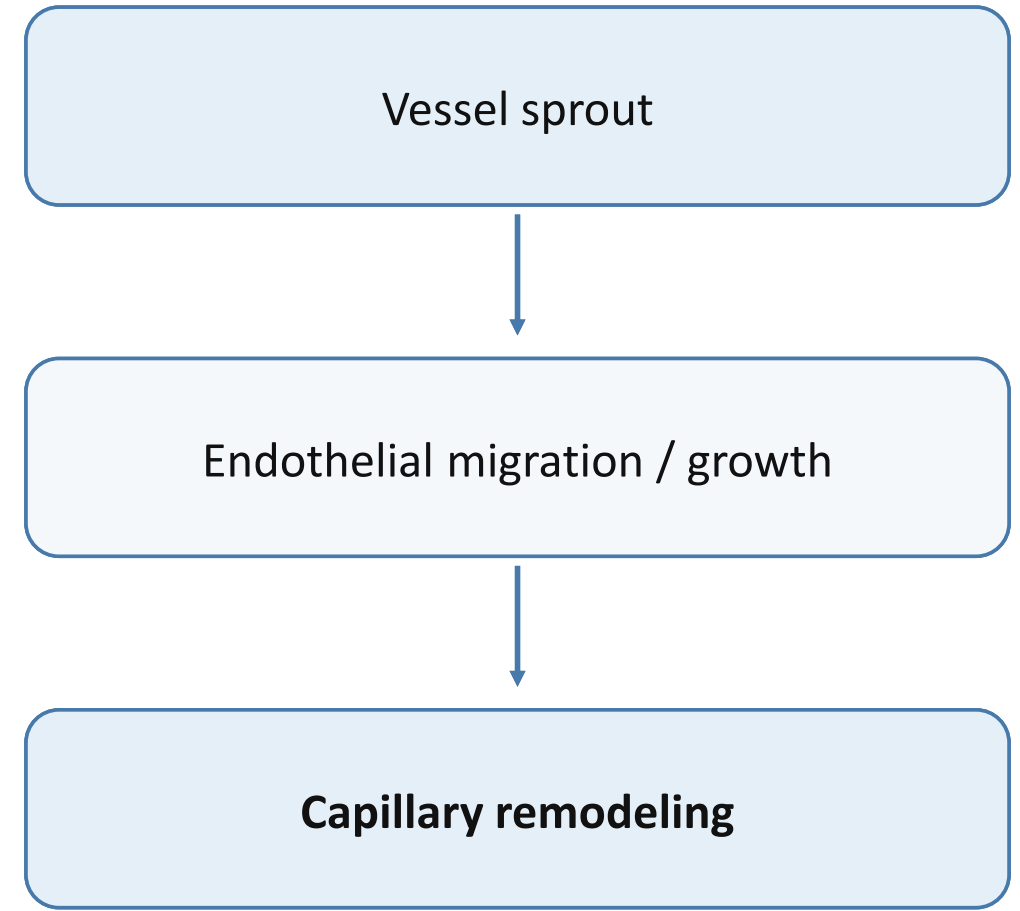
Endothelial cells are active stromal participants

- Endothelial cells are named partners in tumor microenvironment cross-talk.
- Their response to angiogenic mediators changes tissue vascularity.
- The effect is biologically distinct from direct stimulation of cancer-cell division.



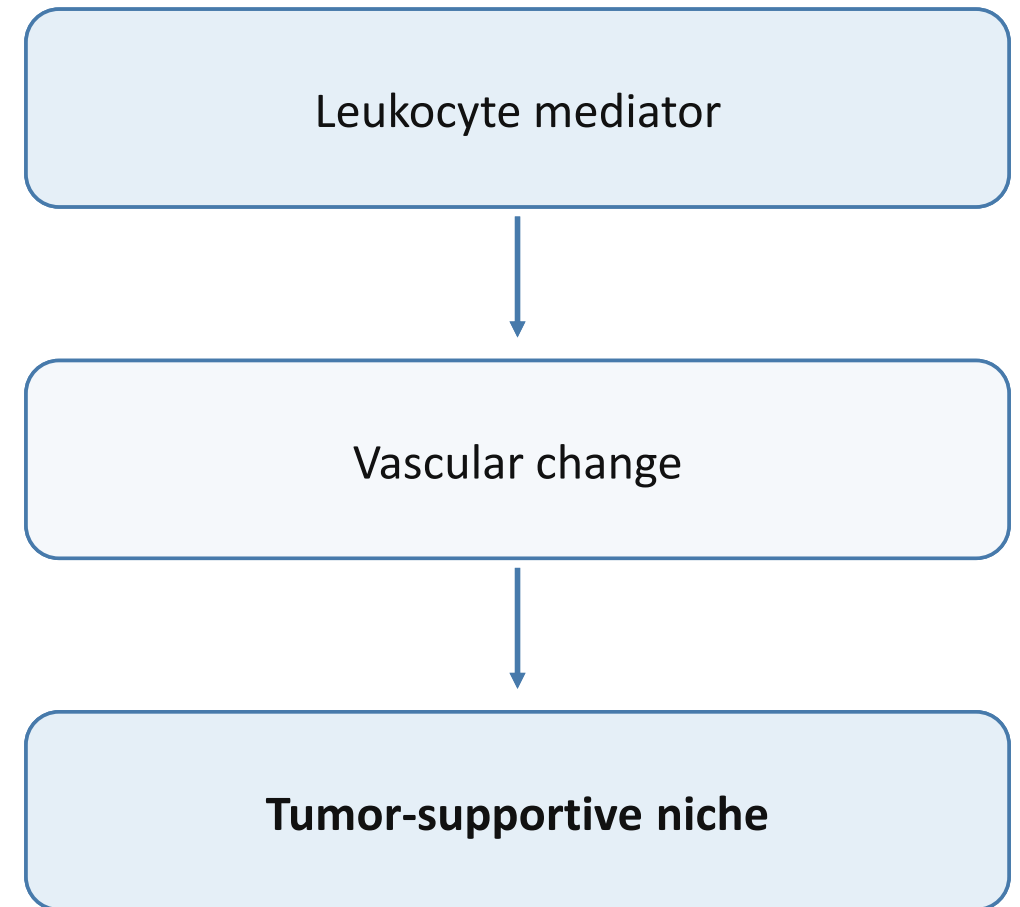
Sprouting angiogenesis: Repair context

- In tissue repair, new vessels can sprout from existing vessels.
- Endothelial migration and proliferation precede tube remodeling.
- Robbins Chapter 3 supplies this normal-process framework.



Angiogenesis can be a malignancy-enabling output

- The inflammatory cell need not itself form a vessel.
- Its secreted mediator can recruit a vascular response.
- Stromal reprogramming indirectly assists tumor progression.



Inflammatory infiltration does not imply antitumor control

Potential host defense

Recognition and cytotoxicity

Effective tumor elimination

Cancer-enabling effect

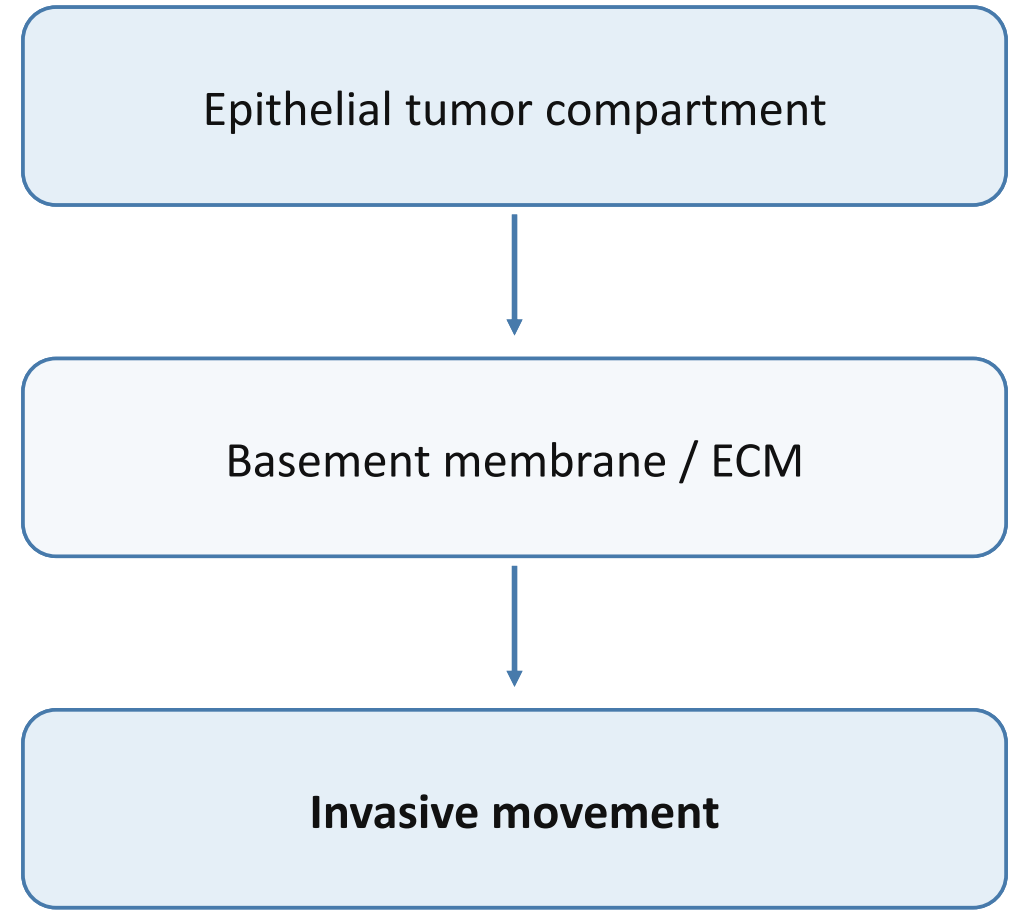
VEGF and stromal remodeling

Expansion support

- A tumor may contain many inflammatory cells and still progress.
- Some of those cells can release angiogenic growth factors.
- The nature of the infiltrate matters more than its mere presence.

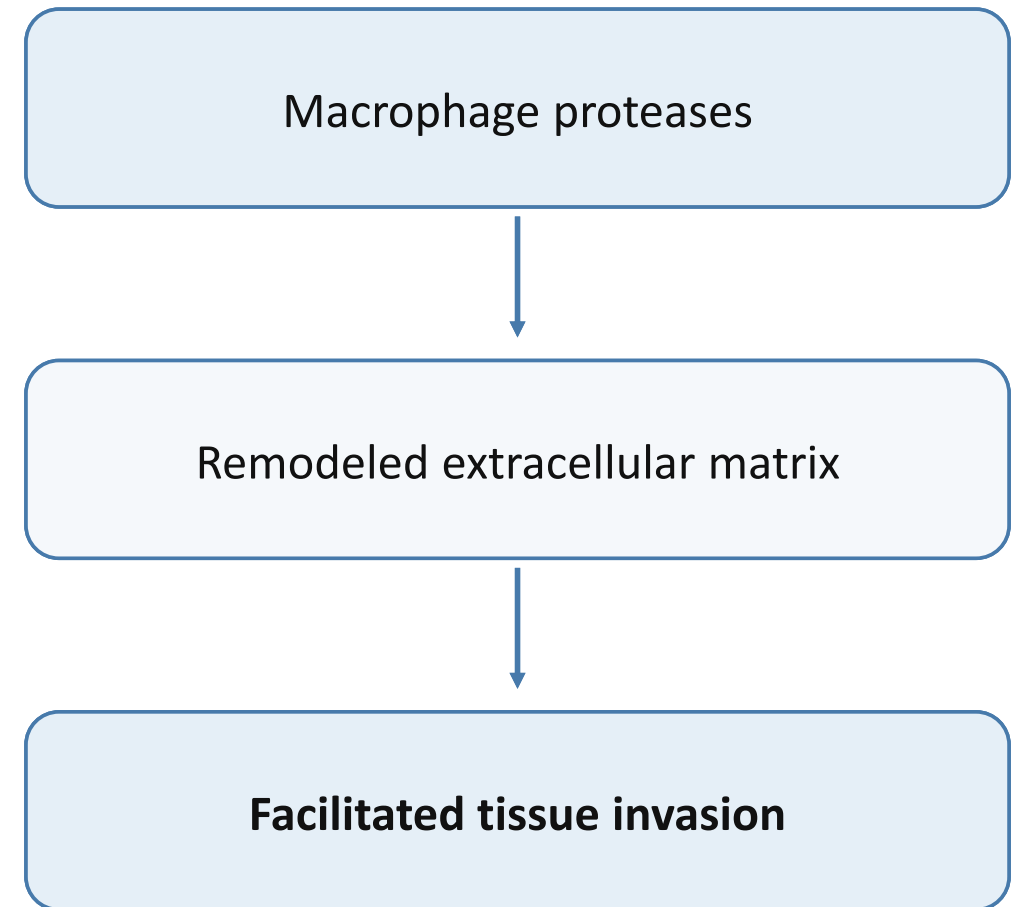
Invasion requires crossing tissue boundaries

- Carcinoma cells must breach basement membrane and interstitial ECM.
- Cell attachment, matrix remodeling, and motility participate.
- Host inflammatory cells can cooperate in these steps.



Macrophage proteases remodel ECM

- Tumor-associated macrophages can release matrix-degrading proteases.
- Remodeling changes resistance of tissues to tumor-cell movement.
- This supports a permissive environment for invasion.



ECM degradation can support invasion by two routes

Structural

Matrix / adhesion cleavage

Barrier altered

Biochemical

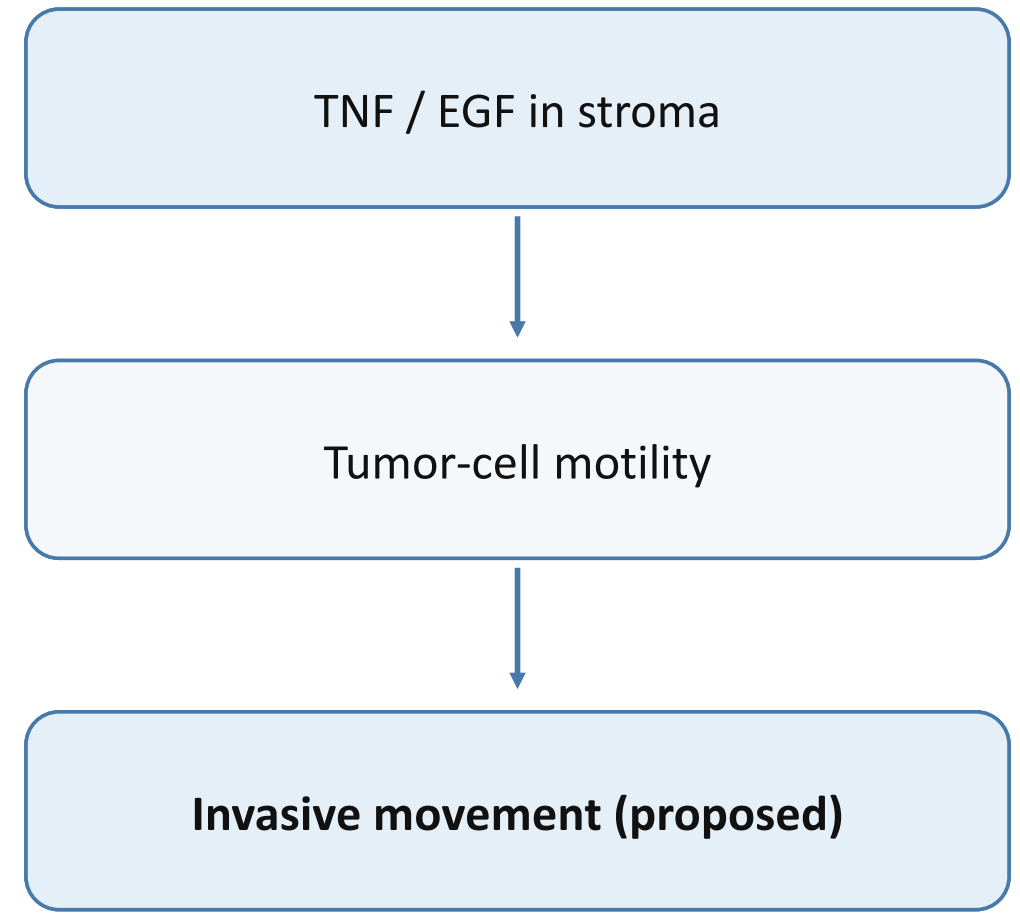
Liberation of bound factors

Cell behavior modified

- Proteolysis can physically modify the matrix barrier.
- Degradation can also release mediators associated with ECM.
- Thus structural and signaling consequences may coexist.

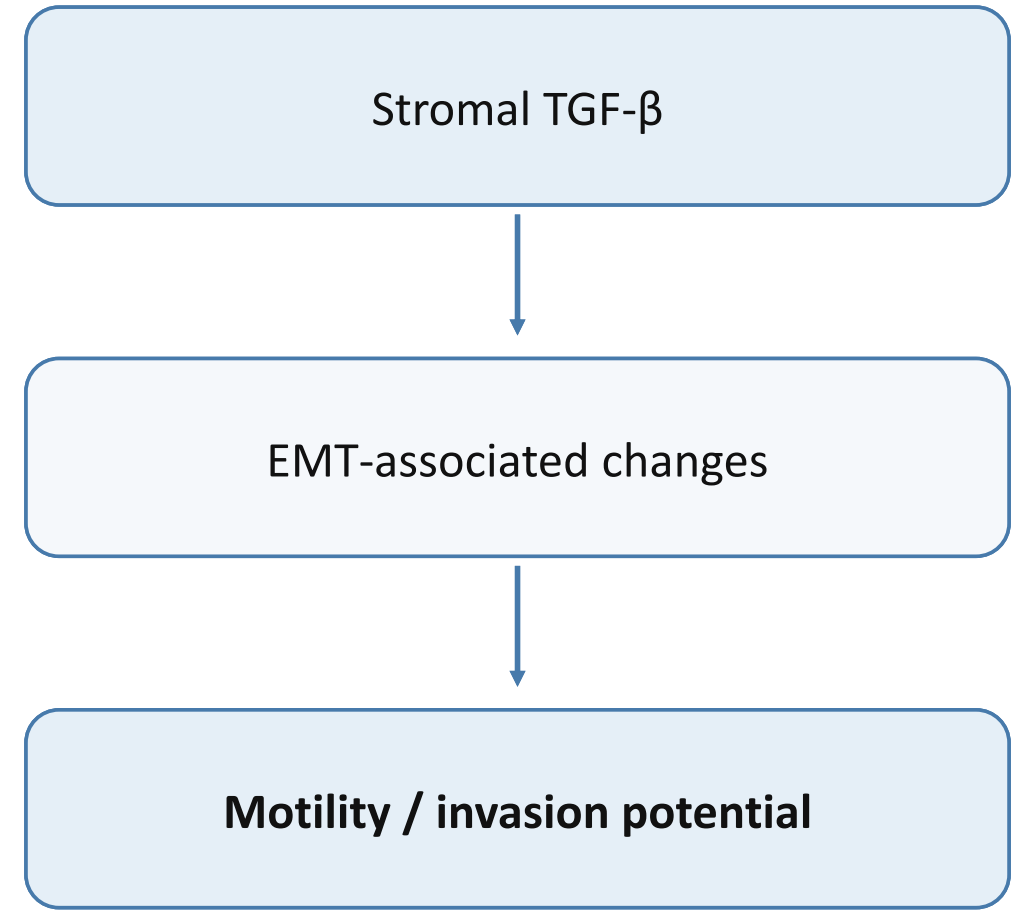
TNF and EGF may stimulate motility

- TNF and EGF are cited as possible motility-promoting factors.
- Their actions are conceptually distinct from matrix degradation.
- Both cell movement and tissue access are required for invasion.



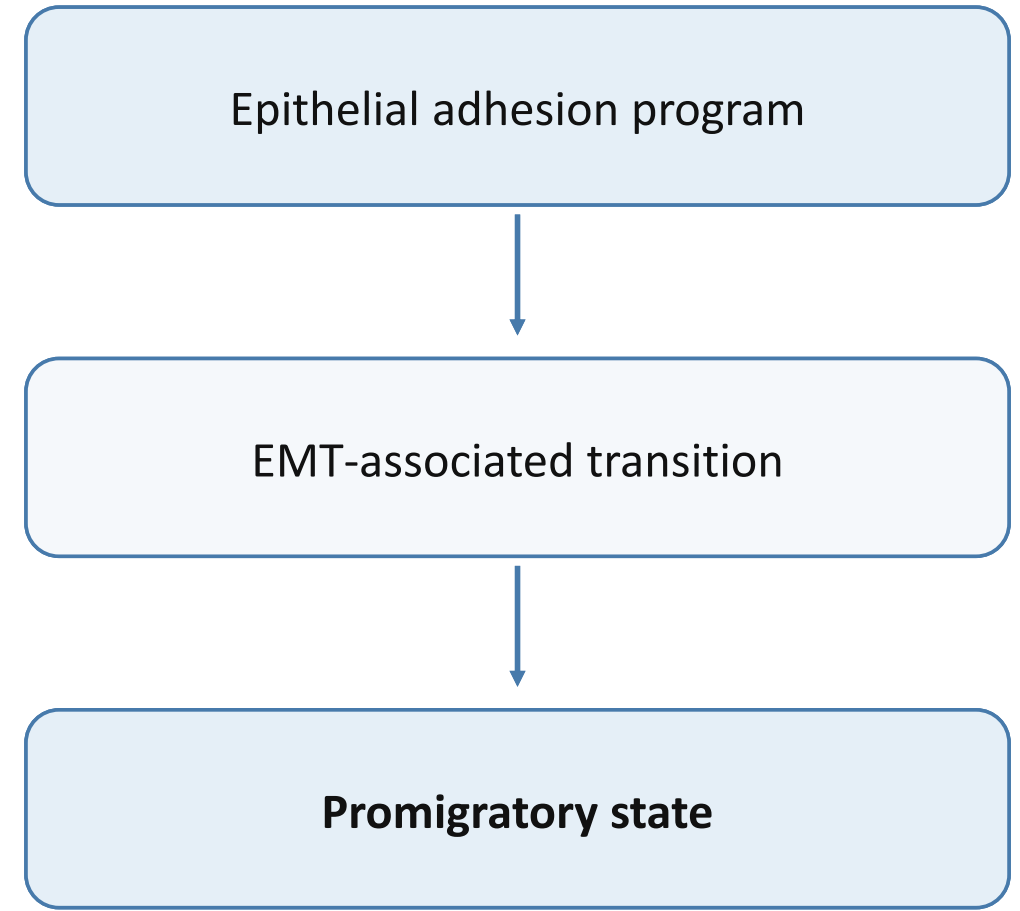
TGF- β may favor epithelial–mesenchymal transition

- Stromal TGF- β is described as a potential EMT-promoting factor.
- EMT refers to acquisition of a more migratory cellular program.
- The source frames its contribution to invasion/metastasis as believed, not universal.



EMT changes epithelial cell phenotype

- EMT with reduced epithelial markers such as E-cadherin.
- Mesenchymal-associated markers may increase.
- These changes are proposed to favor a promigratory phenotype.



Matrix access and motility are separate requirements

Terrain changes

Macrophage proteases

ECM remodeling

Cell behavior changes

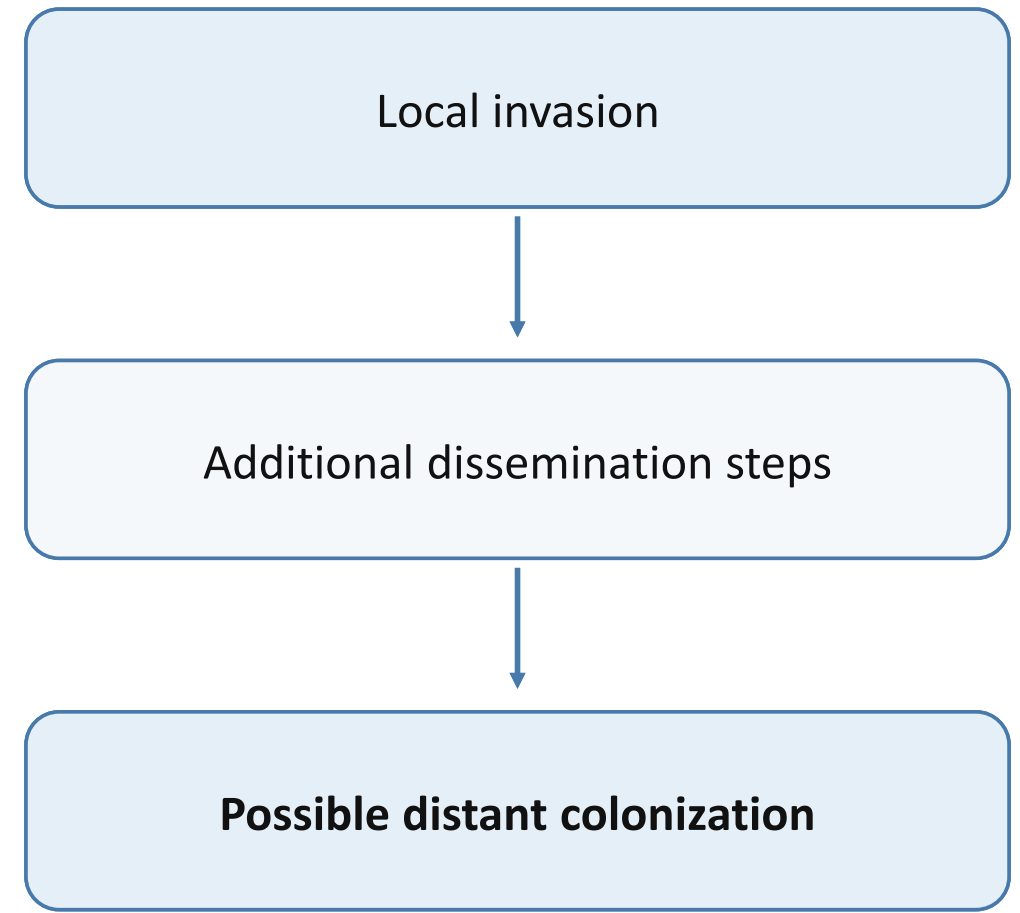
TNF, EGF, TGF- β

Motility / EMT

- Proteolysis changes the terrain through which a cell travels.
- Motility-inducing factors change the cell's movement behavior.
- Their cooperation gives a coherent mechanistic model of invasion.

From invasion to metastasis: Do not overstate

- Invasion is part of the metastatic cascade, not identical to successful metastasis.
- Movement through ECM is only one of several necessary steps.
- The source describes inflammation as contributing, not guaranteeing dissemination.



Applied mechanism: Macrophage-rich invasive front

Macrophage-rich tumor margin

Predicted: ECM remodeling

Not proved: Distant metastasis

Discuss the mechanistic inference and what remains unproved.

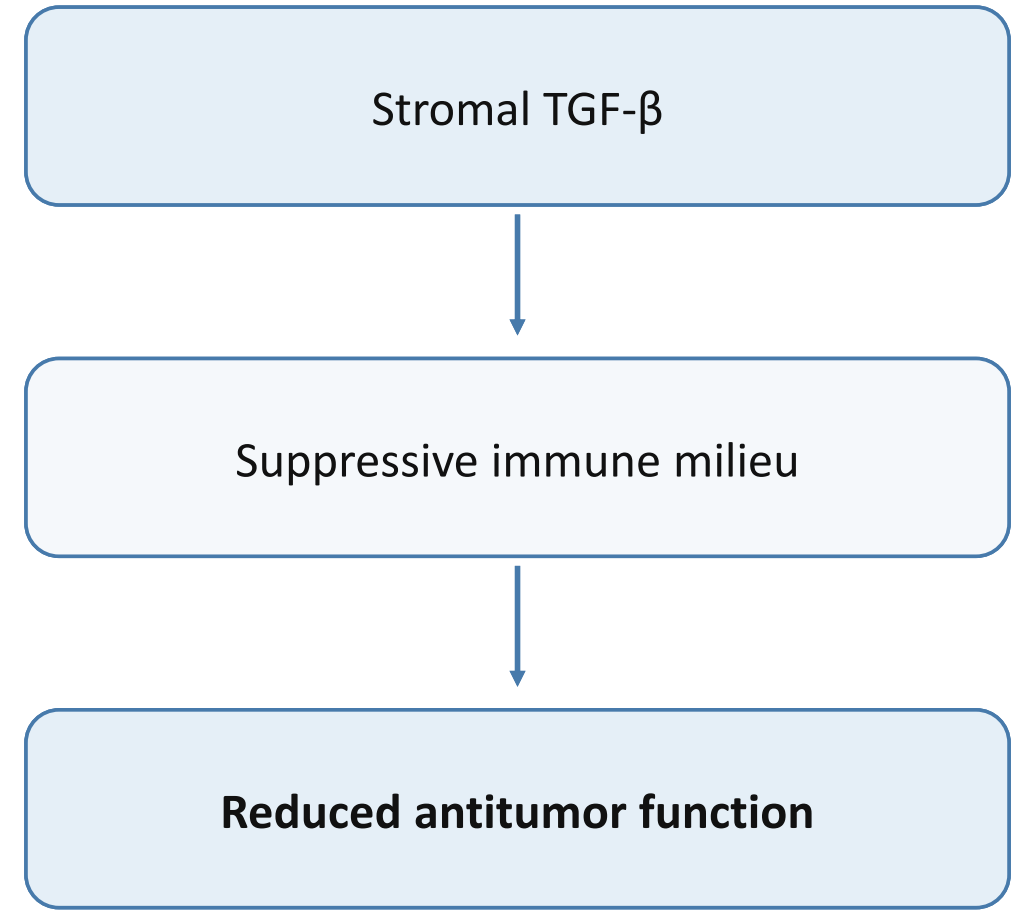
Antitumor immunity and inflammation are not synonymous

Immune control	Immune escape
Antigen recognition	Suppressive mediator networks
CD8+ cytotoxicity	Reduced CD8+ function

- CD8+ cytotoxic T lymphocytes can eliminate antigen-bearing tumor cells.
- Other immune populations can instead support a suppressive microenvironment.
- An infiltrate contains functionally diverse cells.

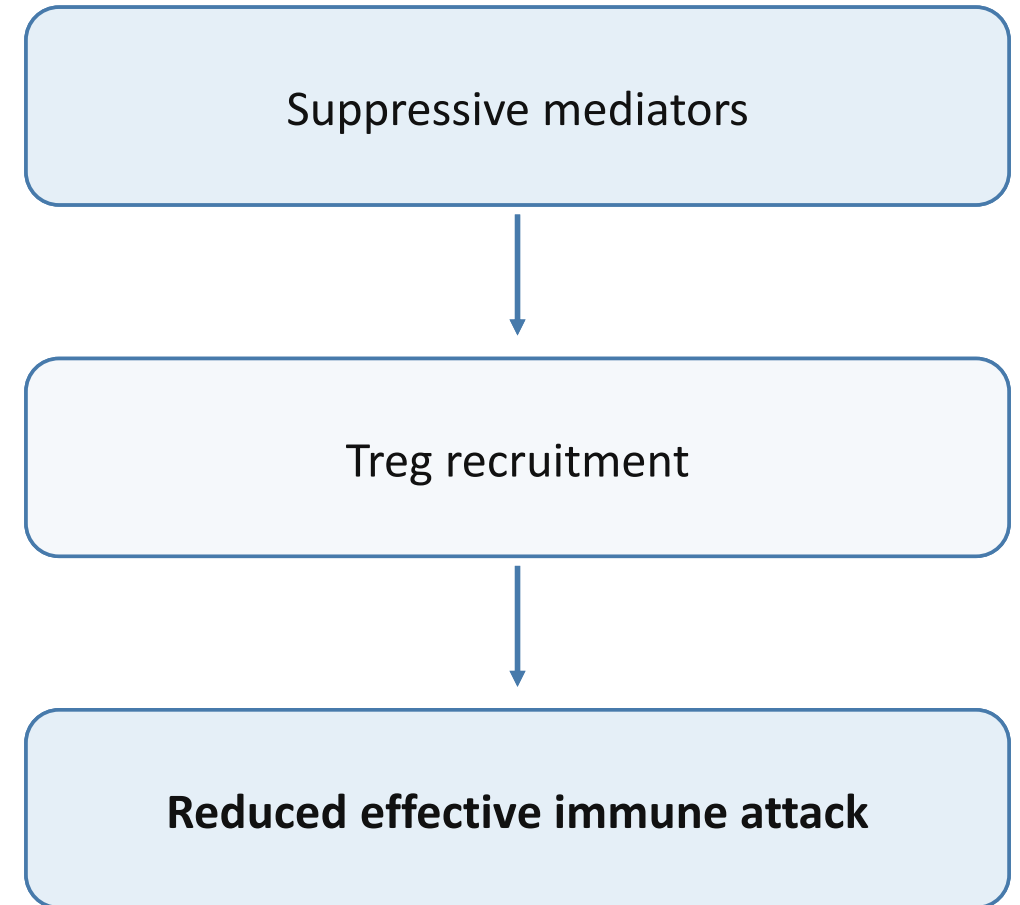
TGF- β is implicated in immunosuppression

- Tumor-associated stromal cells can release immunomodulatory mediators.
- TGF- β is one named example.
- Such signals may contribute to Treg enrichment or cytotoxic T-cell suppression.



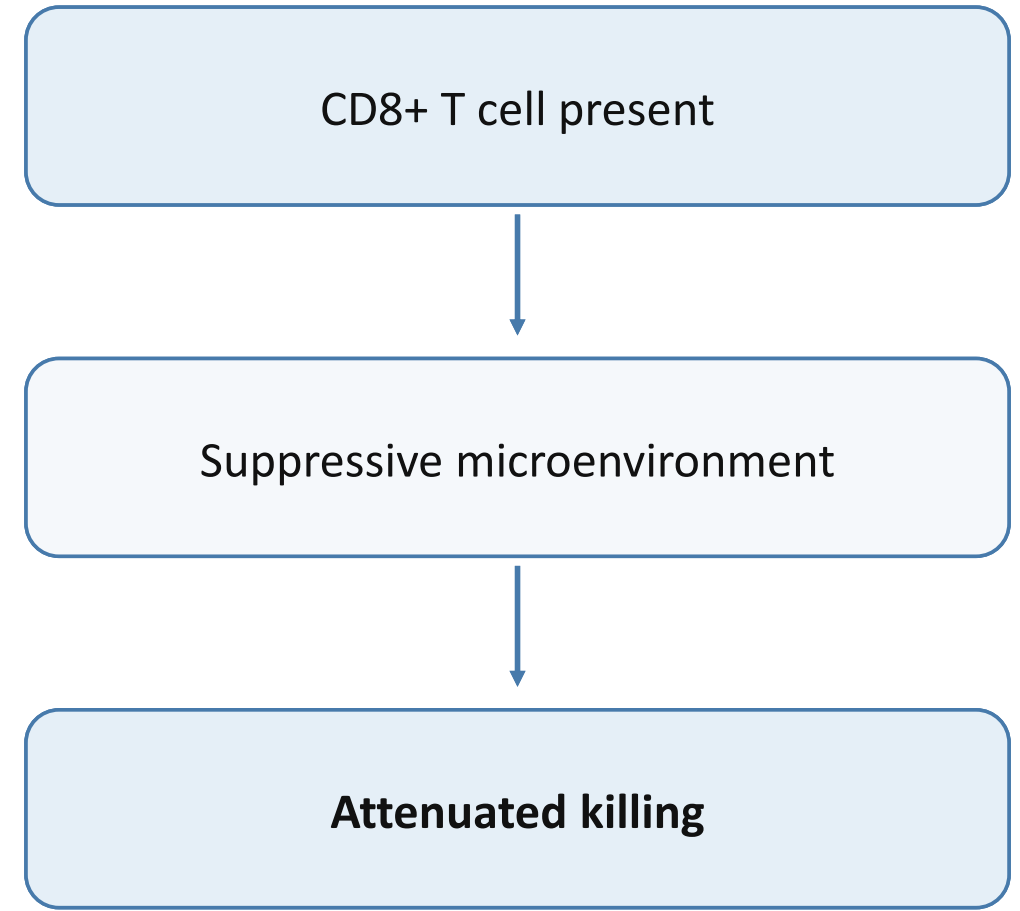
Regulatory T-cell enrichment can impair tumor control

- Stromal mediators may favor recruitment of regulatory T cells (Tregs).
- Tregs are an immunosuppressive component of the tumor milieu.
- Recruitment shifts the balance away from effective cytotoxicity.



CD8+ T cells can be present yet functionally restrained

- CD8+ T cells mediate a major arm of tumor cell killing.
- Locally produced factors may suppress their function.
- Functional state, not only cell count, influences immune surveillance.



Macrophages are not one uniform population

Classical / M1-like

IFN- γ or microbial stimuli

Microbicidal/inflammatory functions

Alternative / M2-like

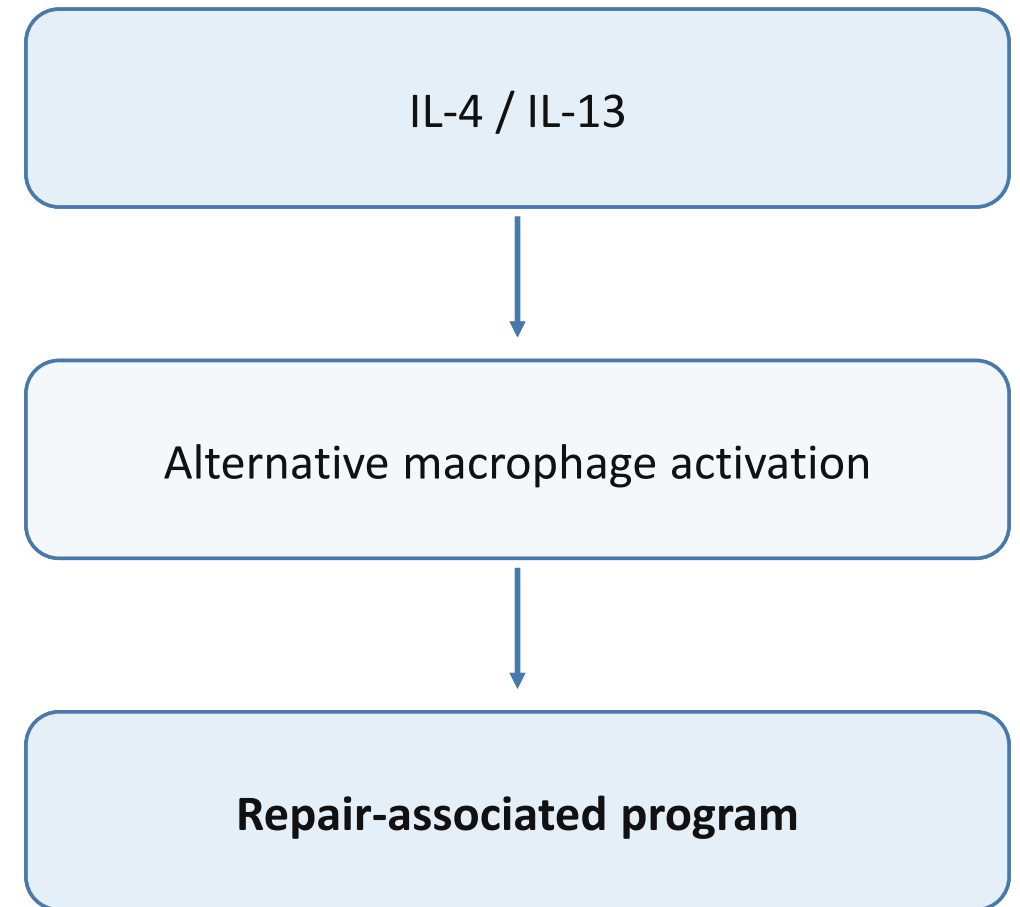
IL-4 and IL-13

Repair and remodeling functions

- Classical (M1) and alternative (M2) activation.
- Their programs emphasize different functions.
- The categories are endpoints of a spectrum, not perfectly exclusive subsets.

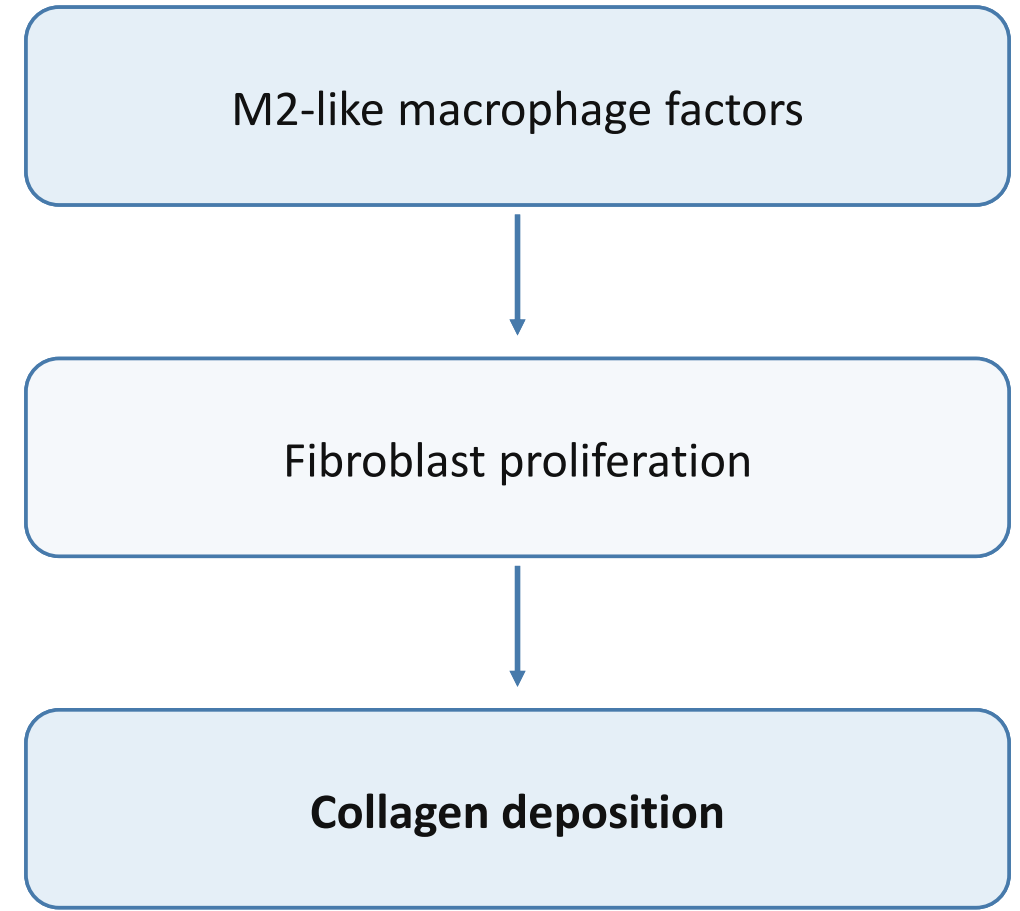
IL-4 and IL-13 promote alternative activation

- IL-4 and IL-13 are named drivers of the M2-like program.
- Alternative activation generally supports tissue repair.
- Tumor-associated M2-like cells can co-opt these physiologic repair functions.



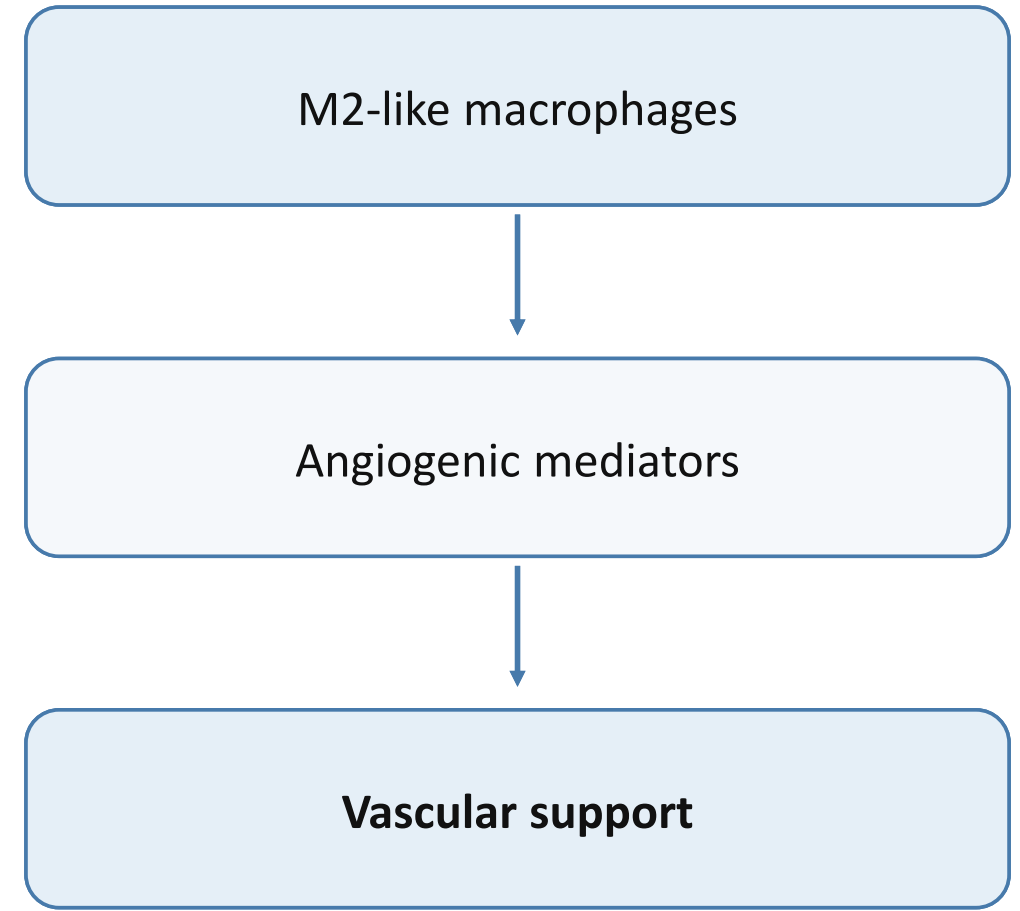
M2-like macrophages can build fibrotic stroma

- Cytokines that stimulate fibroblast proliferation.
- Collagen deposition can follow a repair-associated response.
- These changes are frequently present in invasive tumors.



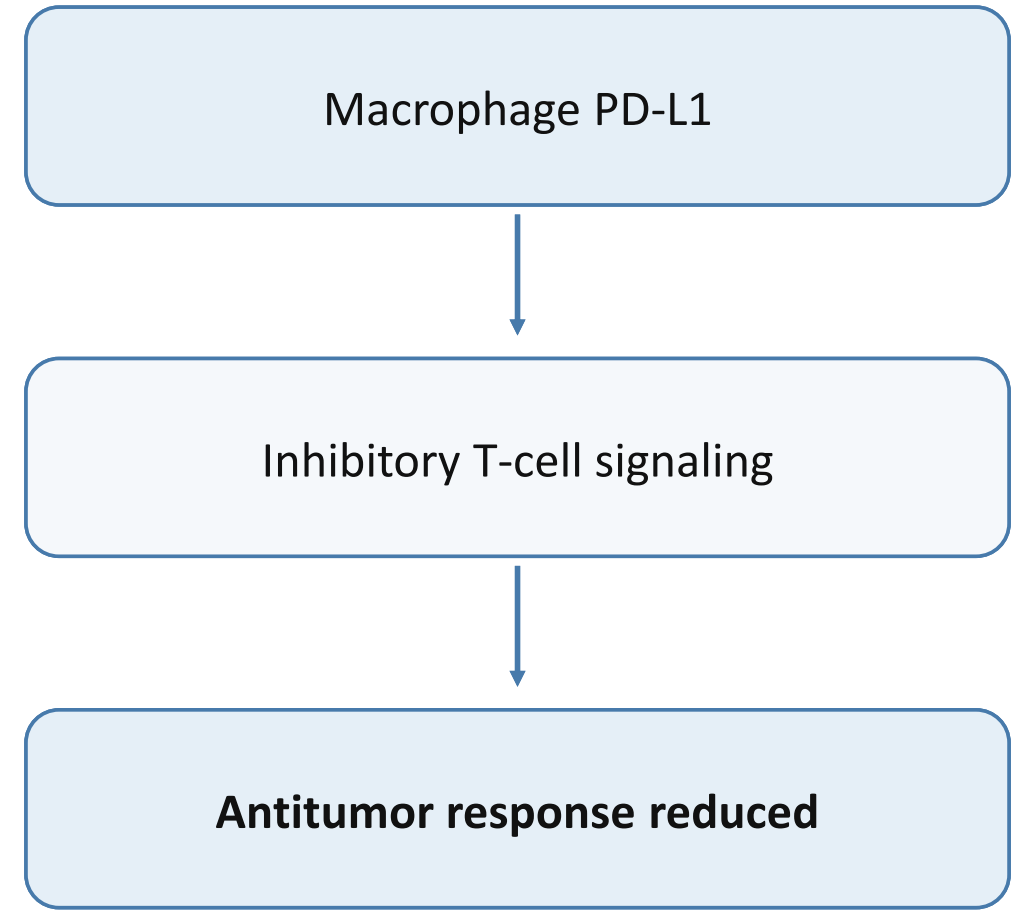
Alternative macrophage activation can favor angiogenesis

- M2-like macrophages can produce proangiogenic cytokines.
- Their effects link immune-cell state with vascular remodeling.
- The result is a possible protumor support function.



Macrophage PD-L1 can suppress effective immunity

- The source describes PD-L1 expression on some macrophages.
- Checkpoint-ligand signaling can inhibit antitumor T-cell responses.
- This is a host-cell contribution to immune evasion.



PD-L1 need not come from the cancer cell

Tumor-cell contribution

Tumor-derived inhibitory factors

Cell autonomous evasion

Stromal contribution

Macrophage PD-L1

Microenvironmental evasion

- Tumor cells can employ checkpoint-associated immune escape.
- Macrophages in the tumor microenvironment may also express PD-L1.
- Cellular source of an immune-regulatory signal matters.

The M1/M2 binary is a teaching simplification

- M1 and M2 represent polar functional states Chapter 3.
- Intermediate macrophage programs are common and hard to classify.
- Avoid identifying every tumor macrophage as exclusively M2.



Phenotypic continuum — not a time sequence

Human evidence and model evidence differ

Animal models

Abundant mechanistic observations

Proof-of-principle

Human tumors

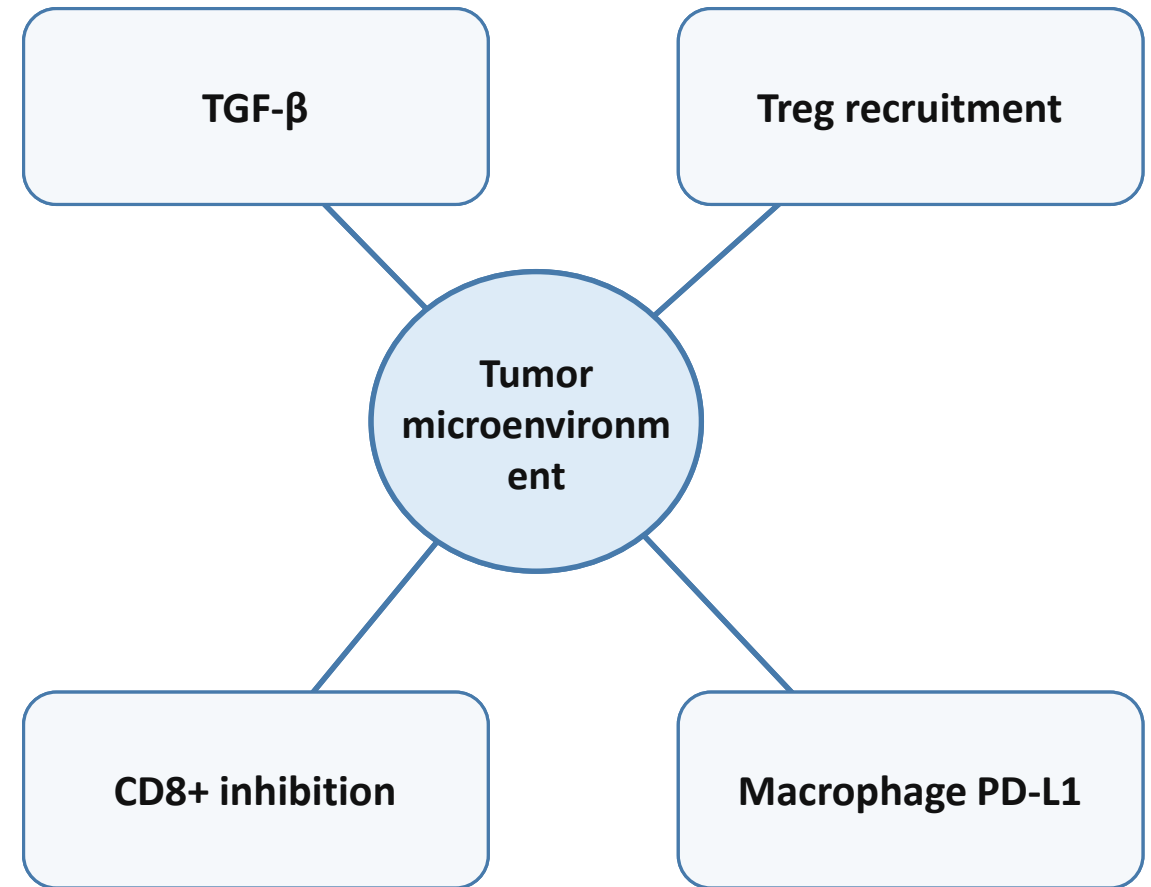
Emerging supporting evidence

Context-dependent interpretation

- M2-like macrophage enrichment is supported strongly in murine models.
- Emerging evidence in human advanced cancers.
- Universal clinical prevalence or causal magnitude is not established here.

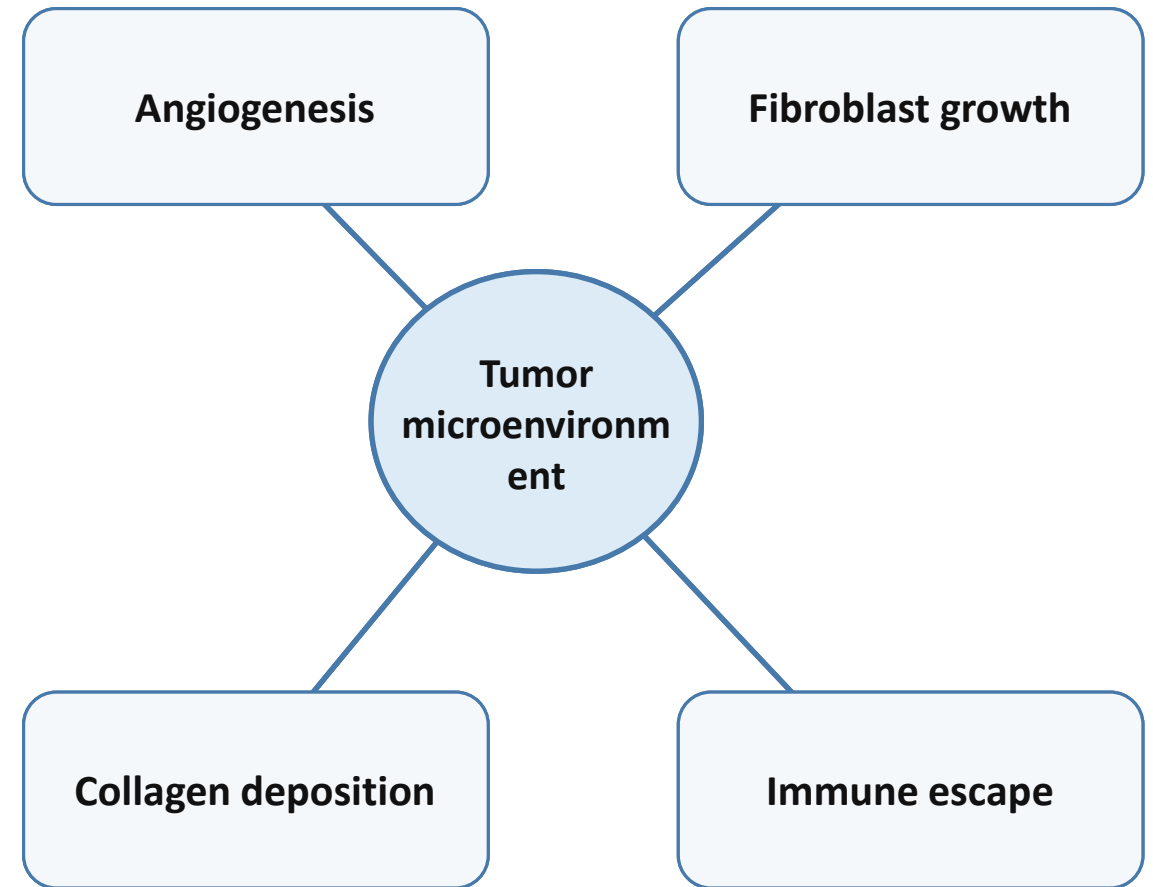
Immune evasion is a multicellular output

- Suppressive cytokines influence Treg recruitment and CD8+ function.
- Macrophage PD-L1 supplies a separate inhibitory mechanism.
- Several pathways can converge on reduced tumor-cell elimination.



One stromal process may affect several hallmarks

- M2-like macrophage signals can promote angiogenesis.
- Fibroblast proliferation and collagen deposition remodel tissue.
- Immunosuppression provides an additional route to tumor persistence.

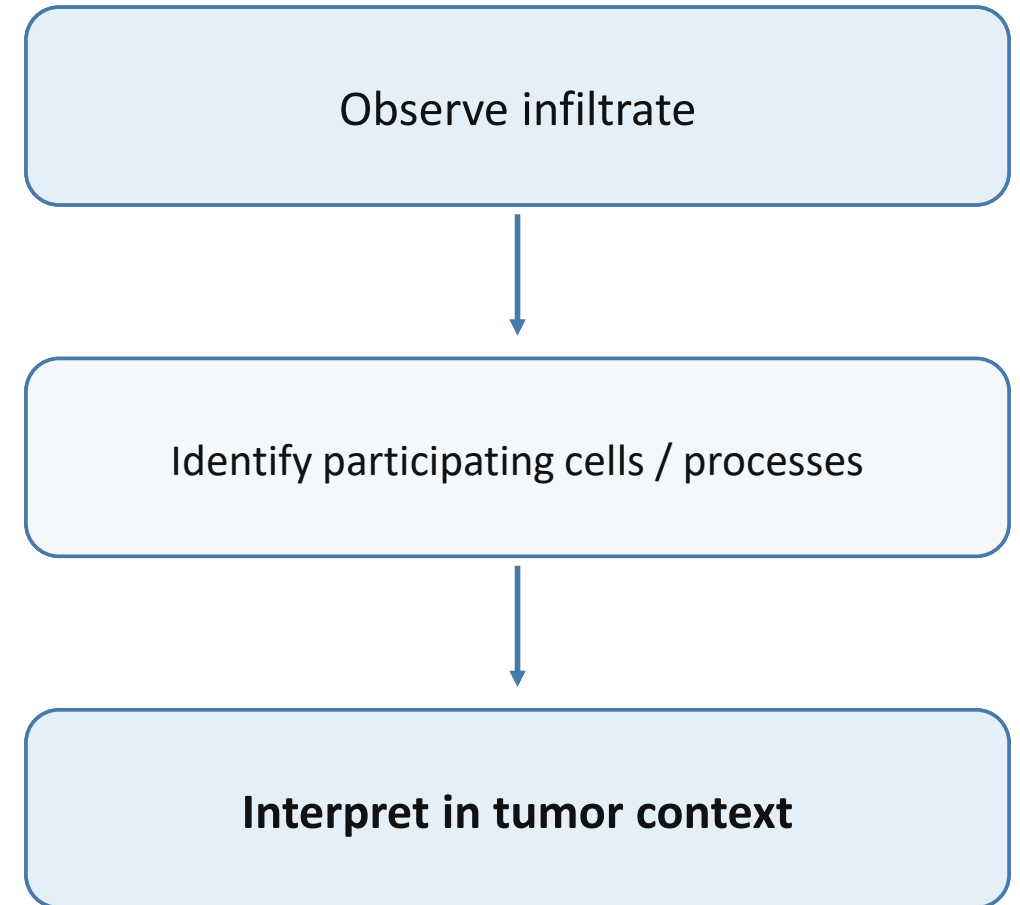


Cancer-enabling outputs: Integrated mechanism map

Inflammatory/stromal input	Immediate process	Cancer-enabling outcome
EGF and related signals	Growth stimulation	Proliferation
Proteases	Adhesion / ECM remodeling	Growth, invasion
Integrin-linked contact	Proposed anoikis protection	Survival
VEGF	Endothelial response	Angiogenesis
TGF- β / Tregs / PD-L1	Immunoregulatory signaling	Immune evasion

Inflammation is not a single diagnostic marker

- A mixed inflammatory infiltrate does not itself define malignancy.
- The source discusses mechanisms, not a diagnostic cell-count cutoff.
- Morphology and clinical context remain necessary for interpretation.



Interpret tumor infiltrates by function

Evidence of function

Mediator / location / cell type

Mechanistic hypothesis

Unsupported shortcut

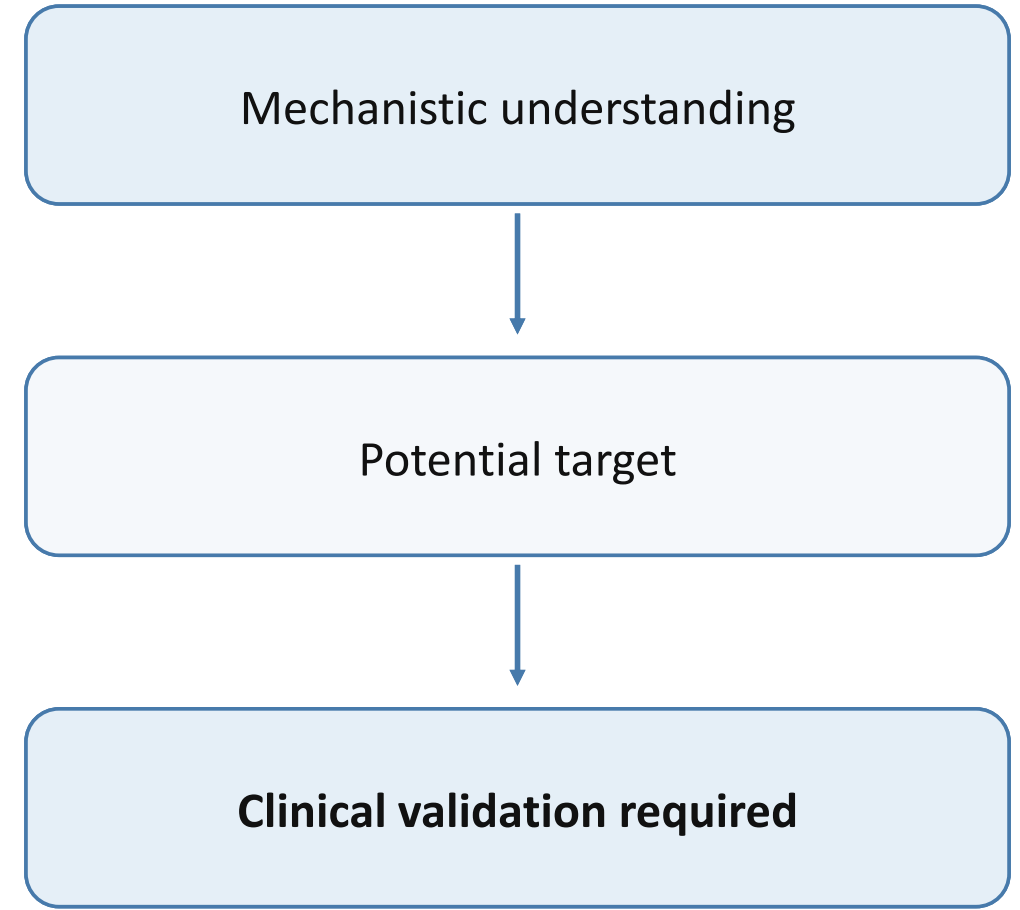
Infiltrate abundance alone

Prognosis or response claim

- Proliferative growth signals and proteases can be growth enabling.
- VEGF-rich environments may support vascularization.
- T-cell suppression differs from successful antitumor cytotoxicity.

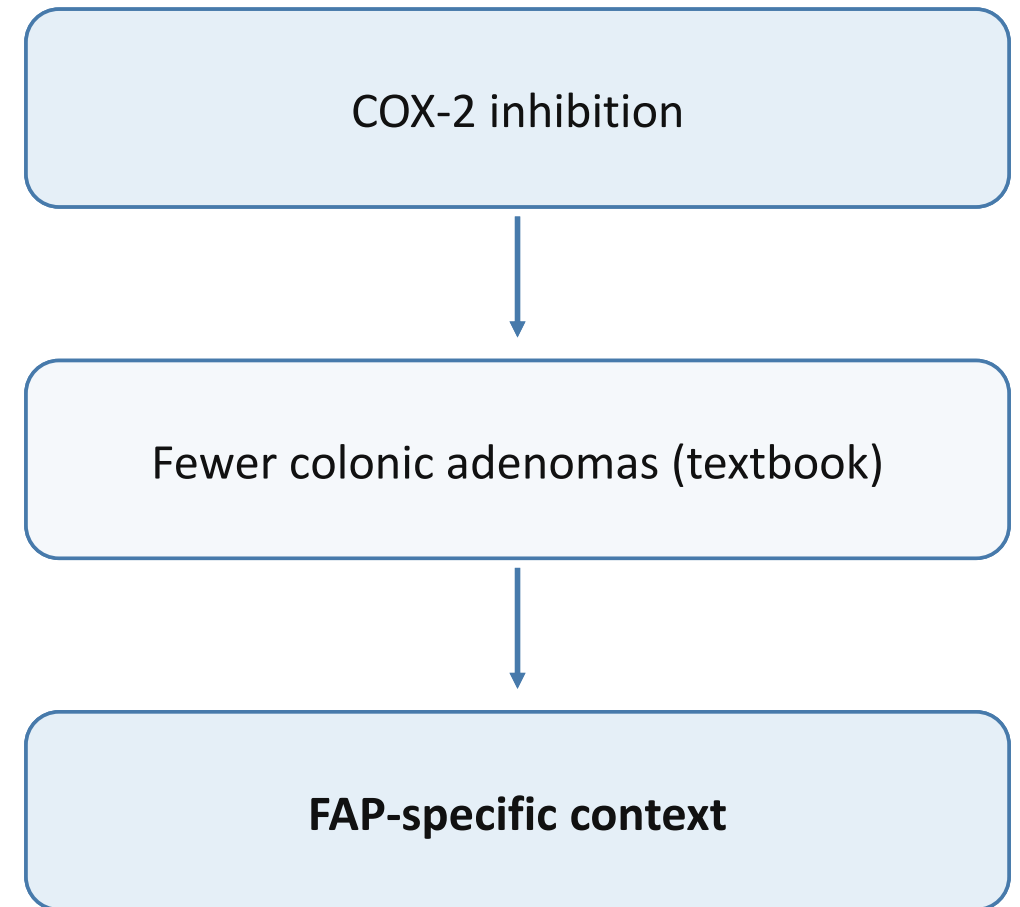
Therapeutic implication: Modulating inflammation

- Interest in interrupting tumor-induced inflammation.
- Potential targets include its mediators and downstream consequences.
- A plausible target is not automatically a proven anticancer treatment.



COX-2 inhibition: Textbook clinical example

- Fewer colonic adenomas with COX-2 inhibition.
- Familial adenomatous polyposis (FAP) is its named context.
- Do not generalize this example to all cancers or current prescribing policy.



Mechanistic promise and clinical efficacy are distinct

Mechanistic rationale	Clinical efficacy
Known mediators and cell populations	Patient-level outcomes
Hypothesis	Needs direct evidence

- Tumor–stroma cross-talk provides biologic treatment hypotheses.
- Human outcomes require disease-specific clinical testing.
- The full mechanism of tumor manipulation remains elusive.

Case exercise: Progressive tumor despite inflammation

Inflammatory infiltrate present

Possible proangiogenic / suppressive roles

Tumor still progresses

Discuss the mechanistic inference and what remains unproved.

Map a mediator to its principal action

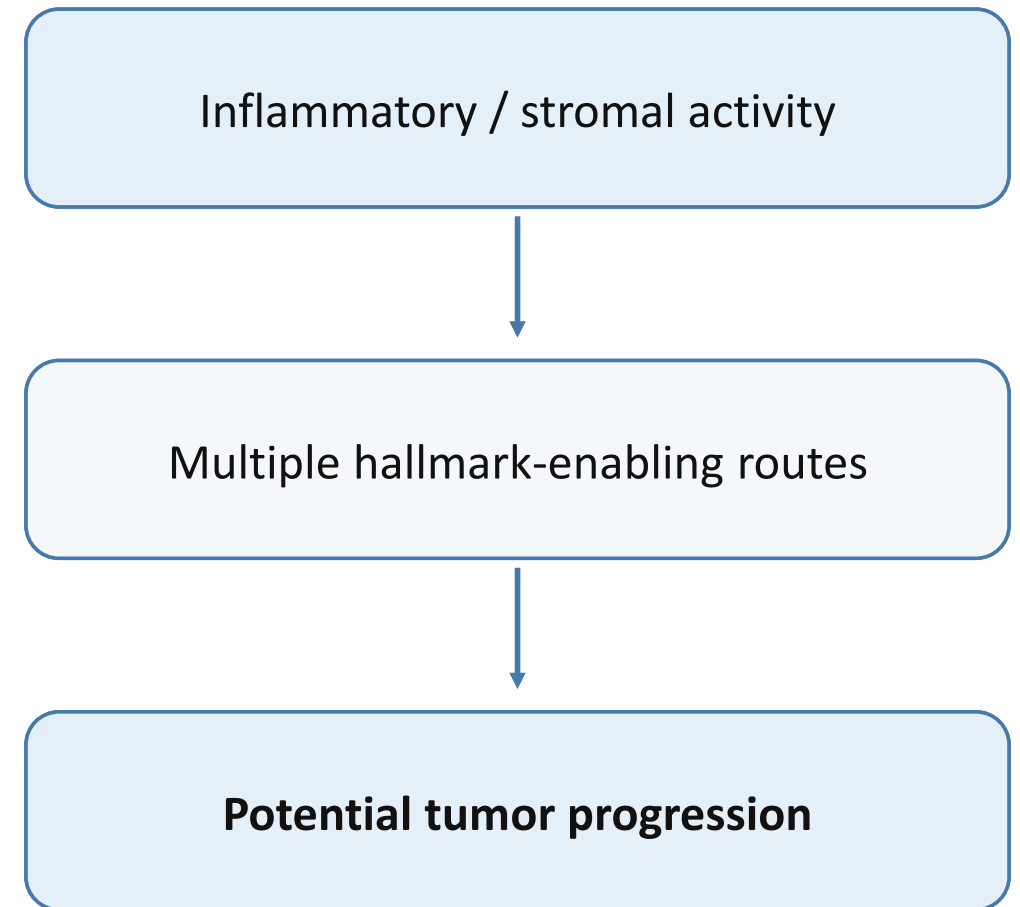
Factor / mechanism	Primary interpretation in this lecture
EGF	Proliferation; possible motility
Proteases	ECM factors / adhesion / invasion
VEGF	Endothelial angiogenic response
TNF	Possible tumor-cell motility
TGF- β	Possible EMT; suppressive immune milieu
Macrophage PD-L1	T-cell inhibition

Five interpretive pitfalls

- Do not equate inflammation with effective tumor elimination.
- Do not treat every macrophage as M2-like or every T cell as cytotoxic.
- Do not equate in vitro/model evidence with routine patient benefit.
- Do not infer metastasis solely from protease-associated invasion.

Teaching synthesis: What inflammation enables

- Leukocytes and activated stroma produce signals and remodel tissue.
- Growth, survival, vessels, invasion, and immune escape are interconnected outputs.
- The net effect is context-dependent; Several proposed pathways remain incompletely resolved.



Selected textbook reading

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026).
- Neoplasia: Cancer-Enabling Inflammation; Evasion of Immune Surveillance; Invasion of Extracellular Matrix.
- Inflammation and Repair: Macrophage Activation; Angiogenesis.